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Review

Nanophytomedicines as Therapeutic Agents for Parkinson's Disease

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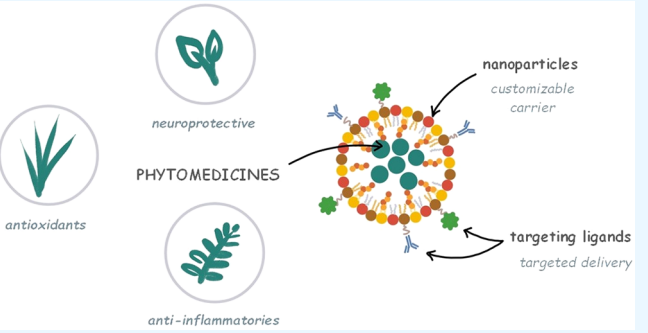
ABSTRACT: Phytochemicals are promising therapeutics for various neurodegenerative disorders, including Parkinson's disease (PD). However, their efficacy, pharmacokinetic properties, and penetration across the blood−brain barrier can be improved using delivery systems such as nanoparticles. We reviewed recently published work in which nanoparticles were used to deliver phytochemicals toward PD treatment. The studies show that nanoparticles not only improve the pharmacological effect of the phytochemicals but also enable targeting to the brain and crossing of the blood−brain barrier. Various ligands were added to the nanoparticles to improve blood−brain barrier transportation. The promising findings from the published studies reveal that more research into nanophytomedicine approaches as therapeutic targets for PD is warranted, especially since they have the potential to protect against key features of PD, including α-synuclein aggregation, mitochondrial dysfunction, and dopaminergic neuronal death. Furthermore, future directions should involve smart designs to tailor nanoparticles for improved therapeutic delivery by modifying their features, such as architecture, surface and material properties, targeting ligands, and responsiveness.



1. INTRODUCTION

Parkinsonism was described in Ayurvedic medicine as early as 300 BC by Maharishi Charaka in his writings, the *Charaka Samhita*.[1] In Western medicine, Parkinson's disease (PD) was first documented by James Parkinson in his treatise, *An Essay on the Shaking Palsy*.[2] PD is characterized clinically by the motor signs of bradykinesia, rigidity, resting tremor, and postural instability, which are accompanied by several nonmotor symptoms, including depression, psychosis, cognitive decline, hyposmia, gastrointestinal dysfunction, autonomic dysfunction, and sleep disturbances.[3] Progression of these symptoms over many years results in high rates of disability and care requirements, thereby having a significant impact on the individual's quality of life. Neuropathological hallmarks of PD are dopaminergic degeneration of the substantia nigra pars compacta, leading to dopamine reduction in the striatum, and the presence of Lewy bodies and Lewy neurites containing accumulations of the toxic α-synuclein protein.[4]

The pathobiological microenvironment of PD involves several different processes. Aggregation of α-synuclein has been attributed to genetic variations leading to its overexpression, as well as post-translational modifications.[5] This overexpression and aggregation result in neurotoxicity, leading to the degeneration of neurons.[6] Oxidative stress has also been shown to play a vital role in neuronal degeneration in PD. Oxidation of proteins, DNA, and lipids in the presence of decreased antioxidants such as glutathione (GSH) has been demonstrated in PD to cause neuronal death.[7] Further sources of oxidative stress arise from the increase in tyrosine hydroxylase and monoamine oxidase levels, both of which are involved in the synthesis and degradation of dopamine.[8] Another source of oxidative stress is lipid peroxidation, which has been shown to be increased in PD.[9] Furthermore, lipid peroxidation has been shown to play a role in α-synuclein neurotoxicity as well as mitochondrial dysregulation.[10,11] Mitochondrial dysfunction is also a key player in the degeneration of dopaminergic neurons in PD, possibly due to it contributing to the high levels of oxidative stress.[12,13] It has also been linked to the initiation of α-synuclein aggregation and results from the dysfunction of PD-linked proteins.[14] Another important aspect of PD pathobiology is inflammation, with several studies providing evidence that there are high levels of neuroinflammation in PD.[14] The overactivation of the central nervous system immune cells such as the microglia leads to increased oxidative stress levels.[15] Indeed, studies have shown that the use of nonsteroidal anti-inflammatory drugs protects dopaminergic cells, thus preventing neuronal death.[15] There is some evidence that overcoming the above cellular stressors, such as protein aggregation, oxidative stress, and

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mitochondrial dysfunction, involves processes that are under the control of protective genes known as vitagenes.[16] Vitagenes play a role in several pro-survival pathways, such as the antioxidant and antiapoptotic pathways, and the dysregulation of the proteins they encode has been implicated in several neurodegenerative diseases such as PD.[16−19]

Between 1990 and 2015, PD was the fastest growing neurological disorder globally considering age-standardized rates for prevalence, disability, and deaths.[20] As PD is an age-related disorder and because the world's population is aging, the number of people with this disorder is expected to increase exponentially. It is estimated that the global PD burden more than doubled from 2.5 million cases in 1990 to 6.1 million in 2016,[21] and if this trend continues there will be approximately 14.2 million people with PD in 2040.[22] Acknowledging this impending global health burden, the World Health Organization published a technical brief in 2022 that highlighted areas for action in developing countries, which include increasing access to and affordability of therapies for PD and promoting the local manufacture of PD drugs.[23]

The current gold-standard drug treatment for PD is levodopa, which, once it crosses the blood−brain barrier (BBB), is converted to dopamine to replenish dopamine levels in the striatum. This drug was developed on the basis of the experiments done by Arvid Carlsson in the 1950s.[24] However, although this drug provides symptomatic relief of motor symptoms, it fails to delay disease progression or halt the death of dopaminergic neurons.[3] It is also often accompanied by adverse effects, including dyskinesias, impulsive control disorders, and drug-induced toxicity.[25] Furthermore, its short half-life leads to undesirable pharmacokinetic properties such as fluctuating plasma levels and clinical response, which is why it is frequently used in combination with other pharmacological agents.[26] Other approved treatments for PD include dopamine agonists, anticholinergics, and monoamine oxidase-B (MAO-B) inhibitors; however, all are accompanied by severe side effects.[27] Nonpharmaceutical treatment options for PD are also available and include the medical procedure deep brain stimulation; although it shows promising results,[28] its is highly invasive, and not all individuals with PD are eligible for it.

As of 2023, there are 139 clinical trials of new drug therapies for PD.[29] Among these, 47 of these trials are in phase I, 70 are in phase II, and 20 are in phase III.[29] The phase II trials include two botanical-based medications, namely pypoestoxide and WIN-1001X.[30] Hypoestoxide is a natural active diterpene phytochemical of *Hypoestes rosea* that was shown to inhibit the activity of inflammatory pathways and modulate PD features.[31] Win-1001X contains the extracts of three plants (*Angelica tenuissima* Nakai, *Dimocarpus longan*, and *Polygala tenuifolia*),[30] which mainly target autophagy and antioxidant mechanisms and reduce neuroinflammation.[32] The clinical trial involves 400, 800, and 1200 mg of WIN-1001X to treat early-stage disease in individuals with PD; however, currently the trial status indicates subject recruitment with no posted results.[30] There is an urgent need to develop drug treatments for PD that have fewer adverse effects and are more effective at targeting the pathobiological mechanisms. Natural products or herbal formulations have recently emerged as promising therapeutic approaches for PD that would provide either independent therapy or neuroprotective support for the existing drugs. Plant-derived drugs have historically played a key role in drug discovery, particularly relating to cancer and infectious diseases,[33] with increasing interest in other therapeutic areas including cardiovascular and neurodegenerative diseases.[34] Plant-derived drugs offer several advantages over commercially available synthetic drugs, such as cost-effectiveness, fewer side effects, easy access, and wide acceptance by the public.[35,36] However, challenges do exist for use of these plant compounds which include structural and acidic pH instability and problems crossing the BBB, all of which lead to reduced therapeutic effects.[35−37] The utilization of nanoplatforms as drug delivery systems has been shown to be a successful approach in overcoming issues relating to the instability, solubility, bioavailability, and pharmacological activity of plant-derived drugs.[33,34,38,39] This has facilitated investigation of the use of plant-derived drugs in therapeutic areas, such as for PD, by permitting transportation of these drugs across biological membranes.[35,38]

2. PHYTOMEDICINES TO TREAT NEURODEGENERATIVE DISORDERS

Phytochemicals, which are the chemicals found in fruits, vegetables, nuts, grains, legumes, and other plant foods that have health-promoting effects, have been receiving increasing attention and have sparked the field of phytomedicine, which is defined as herbal medicine that possesses therapeutic and healing properties.[40] Plant-based medicine has always been a large part of the treatment of diseases. In fact, plants were dried to be used as medicines, so to learn that the origin of the term "drug" comes from the old Dutch word "droog" meaning "to dry" is no surprise.[41] Studies document the use of plant medicine for at least 60 000 years.[42] Western medicine is continually influenced by Chinese and Indian herbal medicine to this day.[40] Unfortunately, a dip was seen in the use of phytomedicines in the Western world, and a shift to synthetic drugs was made the focus of treating diseases. However, in recent years we have seen a shift back to phytomedicines due to their efficacy, accessibility, ability to cause fewer side effects, and cost-effectiveness.[43] Leaves, stems, bark, roots, and fruits are among the various parts of plants that can be used to prevent, delay, and revert symptoms of many different diseases. Interestingly, the active ingredients found in many Western medicines contain compounds isolated from plants.[44]

Plants that have been found to be effective for the treatment of PD include *Tinospora cordifolia*, sesame seed oil, *Hibiscus asper* leaves, *Mucuna pruriens*, *Ginkgo biloba* and black tea.[45−50] These plants, among others, have been found to have various positive effects on locomotor activity, oxidative stress, neuronal degeneration, mitochondrial dysfunction, and α-synuclein aggregation.[45,49,51−53] Polyphenols found in plants possess various properties, including antioxidant, anti-inflammatory, and antiapoptotic activities, which is why they have been gaining interest among PD researchers.[43] Polyphenols such as curcumin, ellagic acid, quercetin and sulforaphane exhibit similar positive effects as the plants listed above.[53−56] A meta-analysis found that when phytomedicines were used in combination with synthetic drugs in PD, a complementary effect was observed.[57] However, although phytomedicines may be the future of PD therapy, their pharmacokinetic properties need to be improved. The limitations include instability, lipophilicity, and molecular size, which are some of the reasons why phytomedicines yield promising results *in vitro* but display less *in vivo* efficacy.[58] Furthermore, as is the problem with many drugs used to treat neurodegenerative disorders such as PD, the BBB also reduces the *in vivo* efficacy of phytomedicines.

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Table 1. Effects of Nano-Phytomedicines on *In Vitro* Parkinson's Disease (PD) Models[a]

cell model (cell line)	therapeutic agent (concentration and duration of treatment)	nanoparticle formulation and functionalization (if applicable)	effects on PD/molecular pathway	was the treatment successful?	main findings	ref
MPP^+-treated (PC-12 cells)	*Curcuma longa* (25, 50, and 100 μg/ml for 30 min)	turmeric-initiated biocompatible gold nanoparticles(Tu-AuNPs)	increased cell viability decreased LDH levels inhibited MDA activity increased GSH levels increased complex I activity decreased apoptotic rates	yes	antioxidative properties of Tu-AuNPs in MPP^+-induced PC-12 cells by balancing or inhibiting ROS generation at oxidative stress by scavenging free radicals and therefore increasing antioxidant defense enzymes	85
MPP^+-treated (SH-SY5Y cells)	schisantherin A (30 μM for 1.5 days)	schisantherin A nanocrystal	decreased p-Akt blocked repression of p-Gsk3β	yes	formulated SA-NCs enhance *in vitro* dissolution and improve oral bioavailability and brain delivery of SA	86
MPP^+-treated (SH-SY5Y cells)	schisantherin A (30 μM for 4 h)	methyoxy poly(ethylene glycol)-*block*-poly((D,L)-lactic-*co*-glycolic acid) (mPEG-PLGA)	decreased p-Akt blocked repression of p-Gsk3β	yes	stronger neuroprotective effects in the MPP^+-induced SH-SY5Y cells, while the mechanism underlying the neuroprotective effects was partially mediated by the Akt/Gsk3β signaling pathway	87
MPP^+-treated (SH-SY5Y cells)	curcumin (0, 10, 20, 50, 100, 200, 500, and 1000 mg/L)	curcumin-loaded polysorbate 80-modified cerasome (CPC) nanoparticles with ultrasound-targeted microbubble destruction (*N*-[*N*-(3-triethoxysilyl)propylsuccinamoyl]-dihexadecylamine	UTMD decreased zonula occludens-1 expression CPC NPs localized to the nucleus TH^+ levels restored decreased α-syn aggregation restored morphology and reduced necrosis increased cell viability	yes	PS 80 surface modification was found to remarkably enhance the penetration of curcumin-loaded cerasomes across the BBB by transcytosis through vascular endothelial cells and, with the additional use of UTMD, BBB opening was induced to allow extravasation of CPC NPs into the brain from the systemic circulation, resulting in an increased uptake of curcumin in the UTMD-treated brain side	88
6-OHDA-treated (SH-SY5Y cells)	naringenin (5−100 μg/ml for 24 and 48 h)	chitosan nanoparticles (NAR NPs)	increased cell visibility pretreatment reduced ROS levels	yes	NAR NPs showed no cytotoxicity at lower concentrations, enhanced neuroprotective ability and antioxidant effect against 6-OHDA-induced neurotoxicity in SH-SY5Y cells	95
MPP^+-treated (SH-SY5Y cells)	puerarin (4.2, 8.4, and 21 μg/mL for 2 h)	PLGA functionalized with D-α-tocopherol poly (ethylene glycol) 1000 succinate (TPGS)	increased cell viability and decreased MPP^+-induced cytotoxicity increased ATP levels increased mitochondrial membrane potential and mitochondrial oxygen consumption rates	yes	no significant cytotoxicity of PU-NCs to MDCK cells. TEER values remained constant regardless of concentrations tested; therefore, PU-NCs did not induce a disruption of the MDCK monolayer barrier integrity or epithelial tight junction opening. pretreatment with PU-NCs increased cell viability with increasing concentrations of the MPP^+-induced SH-SY5Y cells	89
MPP^+-treated (SH-SY5Y cells)	paeoniflorin (1, 5, 10, 20 and 50 μM for 4 h)	black phosphorus nanosheets functionalized with lactoferrin (Lf) and NIR laser irradiation	increased cell viability delivered Paeoniflorin to mitochondria enhanced BBB permeability	yes	encapsulation improved the pharmacokinetic properties of Pae, which were further improved by functionalization with Lf	93

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Table 1. continued

cell model (cell line)	therapeutic agent (concentration and duration of treatment)	nanoparticle formulation and functionalization (if applicable)	effects on PD/molecular pathway	was the treatment successful?	main findings	ref
SNCA-mCherry (SH-SY5Y cells)	curcumin/siRNA (siSNCA)	chitosan NPs coated with SNCA siRNA	enhanced uptake and BBB permeability decreased α-syn expression, mRNA, and aggregation decreased ROS levels	yes	encapsulation improved the pharmacokinetic properties of curcumin and siRNA, which resulted in a reduction of α-synuclein aggregates that was further improved by functionalization	96
MPP^+-treated (SH-SY5Y cells)	glinkgolide B (1−100 μM for 4 h)	hydroxypropyl methylcellulose	increased cell viability increased ATP levels increased mitochondrial membrane potential	yes		90
MPP^+-treated (SH-SY5Y cells)	glinkgolide B (1, 5, 10, or 20 μM for 2 h)	poly(ethylene glycol) (PEG) and poly(ϵ-caprolactone) (PCL) functionalized with Poloxamer 188	increased cell viability		GB-NPs significantly enhanced the cytoprotective activity of GB *in vitro*	91
MPP^+-treated (SH-SY5Y cells)	puerarin (1, 5, 10, 20 and 50 μM for 4 h)	graphene oxide functionalized with lactoferrin (Lf)	reduced number of apoptotic cells increased BBB permeability	yes	Lf-GO-Pue had the potential to protect against neurotoxicity	92
MPP^+/H_2O_2-treated (SH-SY5Y cells)	resveratrol (100 μM)	poly((D,L)-lactic-*co*-glycolic acid) (PLGA) functionalized with lactoferrin	increased BBB permeability increased internalization decreased MPP^+ toxicity reduced ROS levels increased mitochondrial membrane potential	yes	NPs are nontoxic and prevent significant cell death while reducing ROS and improving MMP in MPP^+-treated cells. functionalization with lactoferrin further improved all these conditions	94

[a]Abbreviations: BBB, blood−brain barrier; CPC, curcumin-loaded polysorbate 80-modified cerasome; GB, glinkgolide B; H_2O_2, hydrogen peroxide; Lf, lactoferrin; NPs, nanoparticles; NIR, near-infared; Pae, paeoniflorin; PU-NCs, puerarin nanocrystals; Pue, puerarin; ROS, reactive oxygen species; SA, schisantherin A; SA-NC, schisantherin A nanocrystal; SNCA, α-synuclein gene; TEER, transepithelial/transendothelial electrical resistance; UTMD, ultrasound-targeted microbubble destruction; MMP, matrix metalloproteinases; PD, Parkinson's disease; MPP^+, 1-methyl-4-phenylpyridinium; 6-OHDA, 6-hydroxydopamine; mPEG, methyoxy poly(ethylene glycol); PLGA, poly(lactic-*co*-glycolic acid); PEG, poly(ethylene glycol); PCL, polycaprolactone; P80, polysorbate 80; P188, poloxamer 188; TPGS, D-α-tocopherol poly(ethylene glycol) 1000 succinate; GN, gelatin nanostructured lipid carriers; PLA, poly(lactic acid); AuNP, gold nanoparticles; SPION, superparamagentic iron oxide nanocube; BAP, BA-poly(2-(dimethylamino)ethyl acrylate); BBP, BB-poly(2-(dimethylamino) ethyl acrylate); GSH, glutathione; SOD, superoxide dismutase; TH^+, tyrosine hydroxylase positive.

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Table 2. Effects of Nano-Phytomedicines on *In Vivo* Parkinson's Disease (PD) Models[a]

PD-induced animal model	therapeutic agent (concentration and duration of treatment)	nanoparticle formulation and functionalization (if applicable)	effects on PD/ physiology/molecular pathway	was the treatment successful?	main findings	ref
Wistar rats treated with haloperidol	resveratrol (RV) (2.7 mg/ml per day administered intranasally/intravenously)	nanoemulsions (functionalized with vitamin E)	high scavenging efficiency as determined by a DPPH assay	yes	relatively high *in vitro* and significantly high *ex vivo* trans-nasal mucosal flux	109
			decreased degenerative changes in the RV nanoemulsion-administered group		high RV concentration in the brain when delivered with nanoemulsion through the intranasal route	
			significantly higher levels of GSH and SOD and lower levels of MDA in the RV nanoemulsion-administered group		long shelf life of nanoemulsions as determined by insignificant change in zeta potential and particle size	
hemiparkinsonian rats treated with 6-OHDA	basic fibroblast growth factor (bFGF) (0.2 mg/kg administrated intranasally for 90 min)	gelatin nanostructured lipid carriers (GNL) (functionalized with nonionic copolymer-poloxamer 188 (P188))	bFGF significantly collected in the striatum after intranasal administration and exerted therapeutic effects on the PD rats	yes	GNL efficiently enriched endogenous bFGF in the olfactory bulb and striatum via the nasal epithelium without damage to the mucous membrane	114
			bFGF stimulated dopaminergic function in surviving synapses		dopaminergic function in surviving synapses was stimulated and a neuroprotective role was observed	
male C57BL/6 mice treated with MPTP intranasally	resveratrol (RV) (20 mg/kg/day administered intraperitoneally).	poly(lactic acid) (PLA) nanoparticles (functionalized with polysorbate 80 (PS80)).	MDA levels attenuated	yes	RV-loaded PLA-PS80 nanoparticles protected against MPTP-induced behavioral changes, striatal TH^+ loss and LPO	103
			prevention of MPTP-induced striatal TH^+ protein decrease			
male and female Swiss albino rats treated with haloperidol	*Hypericum hookerianum* (40 mg/kg)	*Hypericum hookerianum* gold nanoparticles (HHGNPs)	significant reduction in LPO and L-glutamate levels	yes	HHGNPs improved motor function, reduced LPO and restored DA and glutamate values in haloperidol-induced mice	113
			significant increase in dopamine level			
male Sprague–Dawley (SD) rats and Zebrafish treated with MPTP	schisantherin A (SA) (4 mg/kg to SD rats by gavage; brain samples collected at 0.5, 1, 2, 4, 8, 12, and 24 h after drug administration)	nanocrystal (NC)	neuroprotective effects such as improved deficit swimming behavior and protective effects on dopaminergic neuron death in MPTP-induced zebrafish	yes	formulated SA-NC enhanced *in vitro* dissolution and improved oral bioavailability and brain delivery of SA	86
	SA (1, 3, or 10 μM in the zebrafish embryo medium for three days)					
male Sprague–Dawley (SD) rats and both sexes of larval zebrafish treated with MPTP	schisantherin A (SA) (4 mg/kg to SD mice. Brain samples collected at 0.5, 1, 2, 4, 8, 12, 16, 24, 36, 48 h).	methyoxy poly(ethylene glycol)-*block*-poly((D,L)-lactic-*co*-glycolic acid) (mPEG-PLGA) (SA-NP)	MPTP-induced deficit of swimming behavior was rescued by the SA-NPs	yes	SA-NPs sustained the drug release profile *in vivo* and remained intact in the intestine and brain after oral administration	87
	SA (1, 3, and 10 μM to zebrafish for 48 h)		SA-NPs significantly prevented MPTP-induced decrease in the TH^+ region		higher uptake of the SA-NPs in the brains of the rats	
			stronger neuroprotective effect than SA alone in attenuating MPTP-induced neurotoxicity		SA-NP-treated Zebrafish showed a protective effect against MPTP-induced dopaminergic neuronal death	
			improved pharmacokinetics of SA using SA-NPs in rats			
mice overexpressed with human α-synuclein	epigallocatechin gallate (EGCG) (100 mg /kg with via tail vein injection for 5, 15 and 30 min and 1, 2, 4, 6, 8, and 24 h)	superparamagentic iron oxide nanocubes (SPIONs) (functionalized with B6 and mazindol (MA) (B6ME-NP)	reduced α-synuclein aggregation in B6ME-NP treated mice	yes	the therapeutic effects of the B6ME-NP on PD-model mice confirm that B6ME-NPs could be a promising agent for early treatment of PD	115
			healthier SN of mice treated with B6ME-NP compared to untreated mice		B6ME-NPs could slow down disease progression	
			DAT and TH^+ expression was the highest in mice treated with B6ME-NPs			

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Table 2. continued

PD-induced animal model	therapeutic agent (concentration and duration of treatment)	nanoparticle formulation and functionalization (if applicable)	effects on PD/ physiology/molecular pathway	was the treatment successful?	main findings	ref
male albino Wistar rats treated with rotenone	resveratrol (RV) (40 mg/kg, orally for 35 days)	resveratrol nanoparticles (NRV)	reversed rotenone-induced changes in rearing behavior and enhanced latency to fall down from the rota rod	yes	treatment with NRV could maintain RV blood levels for a longer time, increasing its bioavailability and, therefore, its pharmacological effect	108
			significant restoration of rotenone-induced SOD, citrate synthase, GSH, and aconitase levels restored mitochondrial complex I activity rotenone-induced MDA levels in the brain were significantly decreased, and CAT levels were increased		NRV showed comparatively better efficacy in attenuating the rotenone-induced PD-like behavioral alterations, biochemical and histological changes, oxidative stress, and mitochondrial dysfunction	
male rats of Wistar treated with rotenone	pramipexole (0.8 mg/ml/day/kg given orally by gavage once daily 30 min before rotenone for 10 days)	pramipexole dihydrochloride-containing nanoparticles	histopathological evaluation of the brain showed reversed rotenone-induced degeneration of the nucleus and cell shrinkage in mice treated with the nanosuspension	yes	more than 85% drug release was observed	110
C57BL/6 mice treated with MPTP	curcumin (15 mg/kg intravenously, with blood samples collected at 0.1, 0.5, 1, 2, 4, 8, 12, and 24 h after injection)	curcumin-loaded cerasome (CPC) nanoparticles (functionalized with ultrasound targeted microbubble destruction (UTMD) and polysorbate 80 (PS80))	protective effect on the MPTP-induced PD mouse model	yes	PS80 surface modification was found to remarkably enhance the penetration of CPC across the BBB by transcytosis through vascular endothelial cells	88
			improved the permeability of curcumin through the BBB model layer owing to the help of UTMD and PS80 modification for the CPC		additional use of UTMD induced BBB opening to allow extravasation of CPC into the brain from the systemic circulation, resulting in an increased uptake of curcumin in the UTMD-treated brain side	
zebrafish embryos and Sprague−Dawley rats were not treated, and mice were treated with MPTP	puerarin (PU) at 6 hpf (25−200 μg/mL to the zebrafish and 4 mg/kg orally to the SD rats and mice)	puerarin nanocrystals (PU-NCs)	PU-NCs exerted a powerful antioxidant capacity	yes	PU-NCs were nontoxic in the zebrafish higher accumulation of fluorescent signals was detected in the intestine and brain of the zebrafish PU-NCs could improve oral bioavailability and enhance drug absorption in SD rats PU-NCs improved locomotor activity as well as movement and balance deficits in mice PU-NCs significantly attenuated MPTP-induced neurotoxicity and the loss of TH^+ neurons in PD mice PU-NCs decreased the production of MDA and increased the activity of SOD and GSH	102
C57BL/6 mice injected with 18 mg/kg MPTP four times with 2 h between each injection	Pae (6 mg/kg via tail vein injection over an eight-day treatment period)	black phosphorus nanosheets (BP-NS) (functionalized with lactoferrin (Lf) and near-infrared (NIR) laser irradiation)	NIR improved BBB permeability	yes	NIR irradiation improved the ability of Lf-BP-NS-Pae to cross the BBB both *in vitro* and *in vivo*	93
			Lf-BP-NS-Pae, Pae, and L-DOPA significantly improved rota rod, pole, and open-field test results		Lf-BP-NS-Pae prevented neuronal damage and associated neurobehavioral deficits in MPTP-treated animals that were also subjected to NIR irradiation	
			Lf-BP-NS-Pae, Pae, and L-DOPA restored MPTP-induced dopaminergic neuron loss		Lf-BP-NS-Pae caused negligible hemolysis, making it suitable for iv delivery	

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Table 2. continued

PD-induced animal model	therapeutic agent (concentration and duration of treatment)	nanoparticle formulation and functionalization (if applicable)	effects on PD/ physiology/molecular pathway	was the treatment successful?	main findings	ref
			BP-NS-NIR enhanced the restoration of MPTP-induced loss of dopaminergic neurons to levels comparable to L-DOPA		BP-NSs were easily captured, mostly by reticuloendothelial system (RES) associated organs prior to renal clearance	
			BP-NS-NIR increased metabolites, decreased MDA production, and increased SOD and GSH levels		BP-NS-NIR did not alter hematological parameters (i.e., no renal, hepatic, or hematological toxicity), nor was there tissue damage, reduction of weight, or a decrease in BBB integrity	
C57BL/6 mice intraperitoneally injected with MPTP (30 mg/mg) for seven consecutive days	curcumin (4 mg/ml dissolved in 100 uL methanol and administered via tail vein injection once every other day, 10 times)	polymers BA-poly(2-(dimethylamino)ethyl acrylate) (BAP) and BB-poly(2-(dimethylamino) ethyl acrylate) (BBP) (functionalized with rabies virus glycoprotein (RVG)) peptide. this study termed the NP RVG-peptide-modified exosome (EXO) REXO for short	increased curcumin accumulation in the brain, colocalizing with TH^+ neurons in the SN for at least 48 h	yes	successful crossing of the BBB	96
			significant increase in Fox p3 in $CD4^+$ T cell expression		REXO NPs acted as an α-syn chelator while decreasing inflammation and improving behavioral characteristics in PD induced mice	
			increase in anti-inflammatory markers (TGF-β and IL-10) and decrease in cytokines (IL-22 and IL- 17)			
			decrease in phosphorylated serine 129 and more α-syn aggregation than EXO			
C57BL/6 mice injected with 18 mg/kg MPTP four times with 2 h between each injection	ginkoglide (GB) (5 mg/kg once per day 7 days before MPTP treatment and then twice a day for 7 days after PD model was established)	nanocrystal using hydroxypropyl methylcellulose	GB-NCs improved performance on rota rod, pole, and open-field tests in MPTP-treated mice	yes	GB-NCs improved the behavioral deficits of mice treated with MPTP	90
			GB-NCs increased levels of dopaminergic neurons, dopamine, DOPAC, and HVA compared to GB alone in MPTP-treated mice		GB-NCs improved neuroprotective effects that can attenuate the loss of TH^+ neurons caused by MPTP	
C57BL/6 mice injected with 18 mg/kg MPTP four times with 2 h between each injection	ginkoglide (GB) (5 mg/kg once per day 7 days before MPTP treatment and then twice a day for 7 days after PD model was established)	poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL) polymers (functionalized with P188)	GB-NPs improved the pole, rota rod, and open field tests results of MPTP-treated mice	yes	GB-NPs improved the oral bioavailability and cerebral accumulation of GB	91
			GB-NPs significantly increased the number of TH^+ neurons		the bioactivity of GB was achieved *in vivo* via mediating its sustained release	
			GB-NPs increased dopamine, DOPAC, and HVA levels			
male Swiss mice treated with 1 mg/kg rotenone once a day from day 8 to day 30, 1 h after treatment with curcumin or nanocurcumin	curcumin (cur) (25 or 50 mg/kg once a day for 30 days)	castor oil, lecithin and cosurfactant PEG 660-stearate	Cur-NPs significantly improved locomotor activities, decreased crossing time, number of slides on the beam walking, and latency time in the pole tests in rotenone treated mice	yes	the effects of Cur-NPs were more pronounced than that of free curcumin, as shown by improved motor performance and prevention of mitochondria complex I inhibition	112
			Cur-NP and Cur-only treatments decreased GPx and GR equally		both forms of curcumin modulated an antioxidant response	
			Cur-NP and cur-only treatments prevented a CAT activity increase			
			Cur-NPs prevented the inhibition of mitochondria complex I activity more than Cur-only			
			no difference in GOT, GTP, and creatine levels between Cur-NP and Cur, indicating no hepatic or renal toxicity			
Drosophila melanogaster wild-type treated with 500 μM rotenone for 7 days	lutein-loaded nanoparticles (2, 6, or 20 μM dissolved in water and given orally for 7 days)	polyvinylpyrrolidone and Tween 80	lutein NPs protected flies from rotenone-induced deficits in the geotaxis and open field tasks while preventing rotenone-induced mortality	yes	lutein NPs improved locomotive activity and survival of flies	111
			lutein NPs protected flies from a decrease in dopamine levels and TH^+ activity induced by rotenone		lutein NPs protected the rotenone-treated flies from oxidative stress, as well as the decreased dopamine levels and reduced TH^+ activity	

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Table 2. continued

PD-induced animal model	therapeutic agent (concentration and duration of treatment)	nanoparticle formulation and functionalization (if applicable)	effects on PD/ physiology/molecular pathway	was the treatment successful?	main findings	ref
			lutein NPs protected flies from a decrease in AChE activity in the head but not the body			
			lutein NPs protected flies from oxidative stress indicators induced by rotenone in both the head and body (SOD, CAT, TBARS and GST)			
C57BL6 mice treated with 40 mg/kg MPTP for 7 days	curcumin nanobubbles (Cur-NBs) (55 mg/mL via tail vein injection once every other day for 6 times)	PLGA (functionalized with 1,2-distearoyl-*sn*-glycero-3-phosphatidylcholine (DSPC) and 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy (polyethylene glycol)-2000] (DSPE-PEG2000) (DSPC +DSPE-PEG-2000 PLGA))	Cur-NBs combined with low-intensity focused ultrasound (LIFU) effectively opened the BBB at various suitable acoustic pressures	yes	Cur-NBs in combination with LIFU significantly increased the BBB permeability of curcumin, which improved behavioral results of MPTP-induced mice	101
			Cur-NBs + LIFU mice had significantly improved results in the rota rod and pole-climbing tests			
C57BL6 mice treated with 18 mg/kg MPTP once every 2 h, four times a day	puerarin (Pue) (5 mg/kg via tail vein injection during the whole 8-day treatment period)	graphene oxide (GO) (functionalized with lactoferrin (Lf))	Lf-GO-Pue increased fall latency, decreased the number of drops, and reduced the turn time and time to reach bottom on day 7	yes	the GO-based nanoplatform effectively limited PD-related neuron damage and other neurobehavioral deficits	92
			Lf-GO-Pue increased the total distance and average speed on day 8		the GO-based nanoplatform showed a significant antioxidant effect	
			all treatments were able to repair neuronal toxicity caused by MPTP treatment and increased dopamine, DOPAC, HVA, 5-TH$^+$, and 5-HIAA levels.			
			all treatments were able to decrease MDA levels			
			all treatments were able to improve GSH and SOD activity, however, Lf-GO-Pue was most effective			
Sprague–Dawley rats treated with 30 mg/kg MPTP daily for 7 days	pueperine (0.05 or 0.1 mg/kg via intragastric administration daily for 30 days)	glycine nanoselenium	treatment increased crossing number, rearing number, and reduced pole test score compared to the MPTP-treated group	yes	glycine nanoselenium improved oxidative stress and behavioral disorders	104
			treatments increased the average optical density of TH$^+$ neurons in the SN of MPTP treated mice		glycine nanoselenium reduced the loss of dopaminergic neurons	
			treatments decreased MDA levels while increasing SOD and GSH-PX activity			
C57BL/6 mice treated with 15 mg/kg MPTP 4 times, 2 h intervals on day 8	resveratrol (RV) (5 mg/kg every other day via tail vein injection from day 1 to 15)	PLGA (functionalized with lactoferrin (Lf))	Lf-NPs increased dopamine and DOPAC levels in MPTP mice	yes	the bioavailability of RV in the substantia nigra and striatum of the MPTP-induced PD mice model was enhanced following the delivery of Lf-conjugated NPs in comparison to free RV and RV-PLGA-NPs	94
			Lf-NPs had a greater effect on the increase in TH$^+$ neurons in the striatum and SN compared to MPTP-only treated mice			
			Lf- NPs showed the greatest decrease in astrocyte activation in the striatum and SN compared to MPTP-only treated mice		Lf-RV PLGA-NPs restored the MMP, thus preventing the degeneration of dopaminergic neurons, improving dopamine levels, and preserving motor function in MPTP-treated mice	
			microglia activation in the striatum and SN was reduced by all treatment groups with NP, with Lf-NPs having the greater effects when compared to MPTP only treated mice			
			Lf-NPs had the greatest effect on the reduction of TNF-α and IL-β levels			
			Lf-NP-treated mice exhibited increased the rearing number, increased time to reach home cage in both the beam and challenging beam tests, and decreased total number of foot slips per step when compared to the MPTP-only group			

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ACS Omega 2023, 8, 42045−42061

Table 2. continued

PD-induced animal model	therapeutic agent (concentration and duration of treatment)	nanoparticle formulation and functionalization (if applicable)	effects on PD/ physiology/molecular pathway	was the treatment successful?	main findings	ref
Wistar albino rats treated with 2 mg/kg rotenone for 5 days and blank microneedle patch for another 7 days	*Bacopa monnieri* microneedle (MN) patch (for 7 days after 2 mg/kg rotenone injections for 5 days)	glyceryl monostearate and Tween 80 (functionalized with two-layered dissolving microneedles)	results of rota rod and actophotometer improved in mice treated with NPs loaded on MN MN-NPs increased GSH levels, CAT, and SOD activity in rats decrease in the number of degenerative neuronal cells in the SN	yes	NPs loaded on MN displayed better neuroprotective activity when compared to the pure drug no signs of skin irritation or sensitivity was observed	107
Swiss albino rats treated with 2 mg/kg rotenone for 5 days and blank microneedle patch for another 7 days	*Bacopa monnieri* microneedle patch (MN) (for 7 days after 3 mg/kg rotenone injections for 5 days)	glyceryl monostearate and Tween 80 (functionalized with two-layered dissolving microneedles)	MN-NP significantly improved pole and rota rod results	yes	improved motor coordination and balance no signs of skin irritation or sensitivity was observed	106
Sprague–Dawley rats treated with 2 mg/kg rotenone daily for 35 days	fisetin (10 mg/kg and 20 mg/kg administered intravenously daily for 35 days)	castor oil, lauroglycol FCC, Tween 80, and transcutol P	PD rats had decreased body weight when compared to control rats, while NP systems significantly increased the body weight of PD rats at low doses NP system improved grip strength, latency, postural instability to cross the beam, number of rears, and overall movement of PD rats NP system increased dopamine levels in PD rats NP system recovered damaged neurons to their characteristic shape in PD rats	yes	NP formulation enhanced the neuroprotection of Fisetin by improving behavioral parameters and dopamine levels	105

[a]Abbreviations: 6-OHDA, 6-hydroxydopamine; BBB, blood–brain barrier; DPPH, 2,2-diphenyl-1-picryl-hydrazyl-hydrate; GB, ginkoglide; MDA, malondialdehyde; MN, microneedle; MPP^+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NC, nanocrystal; NPs, nanoparticles; PD, Parkinson's disease; PLA, poly(lactic acid); SD, Spraque-Dawley rats; RV, resveratrol; SA, schisantherin A; GSH, glutathione; SOD, superoxide dismutase; LPO, lipid peroxidation; TH^+, tyrosine hydroxylase; DAT, dopamine transporter; L-DOPA, levodopa; SN, substantia nigra; TGF-β, transforming growth factor-β; IL-β-10, interleukin-β-10; IL-β-17, interleukin-β-17; IL-β-22, interleukin-β-22; TNF-α, tumor necrosis factor-α; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid; GPx, glutathione peroxidase; GR, glucocorticoid receptor; CAT, catalase; GOT, glutamic oxaloacetic transaminase; GTP, glutamic pyruvic transaminase; AChE, acetylcholinesterase; TBARS, thiobarbituric acid reactive substances; GST, glutathione S-transferase; 5-HIAA, 5-hydroxy indoleacetic acid; GSH-Px, plasma glutathione peroxidase.

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The BBB separates the peripheral blood circulatory system from the central nervous system by tightly regulating the transport of molecules into the brain.[59] It is made up of five distinct components: microglia, astrocyte foot processes, basement membrane, pericytes, and finally endothelial cells (ECs) of capillaries.[60] Each of these components has unique characteristics to aid in the tight regulation of the BBB. The endothelial cells lack fenestrations, which limit the diffusion of small molecules and proteins.[61] In addition, the presence of interendothelial junctions between the ECs prevents the diffusion of water-soluble substances.[61] Finally, the pericytes, astrocytes, microglia, and the basal membrane surround the ECs to provide an extra layer of protection.[60,61] The BBB is responsible for the disposal of waste products, maintaining homeostasis of the brain while acting as a shield by preventing the entry of toxins and pathogens.[62,63] As a result, only about 2% of small-molecule drugs and even fewer large-molecule therapeutics are able to cross the BBB to access the brain.[64] This presents a major challenge for the delivery of drugs to the brain to treat neurodegenerative diseases such as PD. Therefore, before phytomedicines can be used for the treatment of PD, it is important to address their poor pharmacokinetic properties, which may be possible using carriers such as nanoplatforms.

3. NANOPLATFORMS AND NANOMEDICINE

Nanoplatforms is the broad term used here encompassing various types of nanoparticulate structures, such as nanoparticles (NPs) that have at least one dimension within the range from 1 to 100 nm.[65] However, for drug delivery applications, particles that are up to 1000 nm are also considered.[39] The shape of the particles ranges from spherical to cylindrical, conical, tubular, hollow core, spiral, or irregular.[65−68] The particles can either be composed of several layers or be uniform.[65,66] In the former case, the layers consist of (i) the surface layer, which can be functionalized with a variety of small molecules, polymers, metal ions, polymers, or surfactants; (ii) the shell layer, which is chemically different from the core; and (iii) the core layer, which is the central part of the nanoplatform and is referred to as the nanoplatform itself.[65,66] Nanoplatforms are broadly divided into various categories depending on their chemical properties, morphology, and size.[66] These classes mostly include carbon-, inorganic-, and organic-based nanoplatforms.[65,66,69] Organic-based nanoplatforms are extensively used in the biomedical field for drug delivery and cancer therapy due to their nontoxic and biodegradable properties.[65,69,70]

Nanomedicine is the utilization of various nanoplatforms toward health and medicine, specifically regarding the treatment and diagnosis of diseases.[71] Nanoplatforms have revolutionized drug delivery, as their unique features allow therapeutic agents to selectively target organs, tissues, and cells while minimizing the exposure of healthy tissues to these therapeutic agents.[72,73] These features include the ability to modify their surface layer with ligands, antibodies, cations, and other surface modifiers that target specific organelles/organs. Their unique properties provide them with a distinct advantage over other polymeric or macromolecular substances, thus giving them the ability to interact with cells and tissues at a molecular level.[73−75] Nanoplatforms have enabled the investigation of plant-derived drugs within the drug discovery process by eliminating the undesirable properties of phytomedicines, such as poor stability, solubility and absorption.[38] The poor water solubility of phytochemicals is a common reason for the limited use of them in the drug discovery process, as their bioavailability relies on their ability to dissolve in biological fluids, cross membranes, and reach their pharmacological target.[36,37] Phytomedicines can thus be utilized for the treatment of diseases via the use of nanoplatforms, thereby categorizing them under the term of nanomedicines. The role of nanotechnology has contributed significantly to the study of the pathogenesis of PD. Nanotechnology platforms can be used to detect biomarkers of PD such as dopamine loss,[76,77] α-synuclein aggregation,[78] and drug delivery,[79] as well as to aid in improved imaging technologies.[80]

Another important feature of nanoplatforms is their ability to improve the BBB permeability of drugs, thus increasing the chances of delivering the drug directly to the brain. Due to their ideal size, unique physiochemical properties, and ability to be further functionalized for targeted uptake, nanoplatforms have shown great potential in being able to carry drugs across the BBB.[81] For example, polymeric nanoplatforms are able to gain access to the brain through receptor-mediated transport, adsorption-mediated transcytosis, or large amino acid transporter (LAT1).[82] The small size and lipophilicity make it possible for lipid-based nanoplatforms to cross the BBB, while particles between 5 and 200 nm use their small size to gain access across the BBB.[79,83]

There are at least 100 nanomedicines that are approved for use by the United States Food and Drug Administration (FDA) and are available on the market.[39] Currently, there are no nanomedicines in clinical use for PD.[84] However, at least four nanomedicines for PD where the drug is delivered by a polymer nanoparticle entered clinical trials in 2022.[39]

4. USE OF NANO-PHYTOMEDICINE IN PD

Given the rationale above, the use of phytomedicine and nanomedicine is clearly an attractive emerging therapeutic approach in the treatment of PD. To identify and summarize what work has been published in this area to date, we conducted a literature search (on September 5, 2022) of the Scopus database and found 675 articles using the following terms: "Parkinson's disease" AND "Nanoparticles" AND "Therapy OR Treatment". After removing review articles, book chapters, short surveys, and other nonrelevant literature, we identified 27 original research articles that used nano-phytomedicine approaches in overexpression α-synuclein- or toxin-induced models of PD, which are summarized in Tables 1 and 2.

4.1. *In Vitro* Studies of Nanoplatforms and Phytomedicines against PD. Out of the 27 articles, 12 involved *in vitro* studies (Table 1). All but one study, which used PC-12 cells,[85] used the SH-SY5Y neuroblastoma cell line. In nine of the studies, the PD model was created using the toxin MPP^+,[85−93] one used both MPP^+ and H_2O_2,[94] and the remaining two articles used 6-OHDA[95] or an SNCA plasmid to overexpress α-synuclein.[96] The phytochemicals used included curcumin/*Curcuma longa*,[85,88,96] ginkgolide B,[90,91] schisantherin A,[86,87] naringenin,[95] puerarin,[89,92] paeoniflorin,[93] and resveratrol,[94] all of which have been previously shown to be promising therapeutic agents for PD. Seven of the studies made use of polymeric NPs,[87,89−91,94−96] only one study used a lipid-based NP,[88] and one used metallic-based NPs.[85] The NPs used include gold (AuNPs),[85] nanocrystals (NCs),[86] methyoxy poly(ethylene glycol)-*block*-poly((D,L)-lactic-*co*-glycolic acid)

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(mPEG-PLGA),[87] *N*-[*N*-(3-triethoxysilyl)propylsuccinamoyl]-dihexadecylamine cerasomes,[88] chitosan,[95] black phosphorus nanosheets,[93] hydroxypropyl methylcellulose,[90] poly(ethylene glycol) (PEG) and poly(ε-caprolactone) (PCL),[91] and finally graphene oxide.[92] In these studies, all of the therapeutic agents tested were able to alleviate the effects of the toxin, as summarized in Table 1. Curcumin decreased α-synuclein aggregates, restored cellular morphology, and decreased the levels of reactive oxygen species (ROS) and apoptosis.[85,88,96] Puerarin and glinkgolide B were able to increase ATP levels as well as mitochondrial membrane potential and respiration rates.[89−91,93]

Importantly, all of the studies were able to show that encapsulation of the phytochemicals in NPs improved the neuroprotective effects of the phytomedicines when compared to the unencapsulated phytomedicine. Three of the studies were able to show that NPs improved the BBB permeability (a problem with most drugs) of the phytomedicines.[92−94] These studies used the bEnd.3 or HBMEC cell lines, as they display structural and functional properties similar to those of the BBB.[97] Black phosphorus, graphene oxide, and PLGA NPs were all able to increase the BBB permeability of their encapsulated phytomedicines by 2-, 1-, and 2-fold, respectfully, when compared to the free phytomedicine.[92−94] To improve the permeability, these studies functionalized the NPs with lactoferrin, which was able to further increase the BBB permeability by 7-, 2-, and 17.5-fold when compared to NPs without lactoferrin.[92−94] Another study developed a smart NP approach to improve the BBB permeability of curcumin and small interfering RNA targeting SNCA. This system was created by a rabies virus glycoprotein (RVG) peptide-modified exosome (EXO) curcumin/phenylboronic acid-poly(2-(dimethylamino)ethyl acrylate) nanoparticle/small interfering RNA targeting SNCA (REXO-C/ANP/S) NP system.[96] Another three studies used polysorbate 80 (P80)[88] and D-α-tocopherol poly(ethylene glycol) 1000 succinate (TPGS)[89] or poloxamer 188 (P188), which have been previously shown to improve the release profile and BBB permeability of NPs; however, this was not assessed in these studies.[98−100] In addition to the BBB permeability, black phosphorus NPs were also able to improve the effects of paeoniflorin by restoring the cell viability of MPP^+-treated cells.[93] PLGA NPs were also able to increase resveratrol's ability to restore cell viability, mitochondrial membrane potential, and ROS levels, which were further increased by functionalization with lactoferrin by 25-, 20-, 1.2-, and 2-fold respectively.[94] Finally, mPEG was used in one study to prevent immune detection; however, this was not tested in the *in vitro* models used in this study.[87]

4.2. *In vivo* Studies of Nano-Phytomedicines against PD. Table 2 shows the potential therapeutic effects of nanophytomedicines in the 24 studies that involved *in vivo* PD models. Parkinsonism or PD-related symptoms were induced using neurotoxins, of which MPP^+[86−88,90,92−94,96,101−104] or rotenone[103,105−112] were the most common. The *in vivo* models that were treated with neurotoxins included rats,[86,87,102,104,108−110,113,114] mice,[88,90−94,96,101−103,112] zebrafish,[86,87] and *Drosophila melanogaster*.[111] Three of the studies used more than one animal model, since they investigated both drug release properties and the therapeutic effects of the drug.[86,87,102] The phytochemicals that were most frequently used in these studies were resveratrol (concentrations ranging from 5 to 40 mg/kg)[94,103,108,109] and curcumin (concentrations ranging from 15 to 50 mg/kg).[88,96,101,112] These phytomedicines, as well as others mentioned in Table 2, were encapsulated in the following NPs: gelatin nanostructured lipid carriers (GNL),[114] poly(lactic acid) (PLA) NPs,[103] AuNPs,[113] NCs,[86,90,102] mPEG-PLGA NPs,[87] Superparamagentic iron oxide nanocubes (SPIONs),[115] cerasomes,[88] black phosphorus nanosheets,[93] BA-poly (2-(dimethylamino)ethyl acrylate (BAP) and BB-poly(2-(dimethylamino) ethyl acrylate (BBP) polymers,[96] PEG and PCL polymers,[91] PLGA,[101] graphene oxide,[92] and glycine nanoselenium.[104] The most common route of administration of the phyto-nanomedicines was tail vein injections,[92−94,96,101,115] followed by gavage,[86,87,90,91,110] oral,[102,108,111,112] intravenous,[88,105,109] intranasal,[109,114] intraperitoneal,[103,104] or a microneedle patch administration.[106,107] The duration of the treatments ranged from 5 min to 35 days. Treatment with the therapeutic agents used in these studies demonstrated protective effects, with the majority showing an increase in glutathione (GSH)[92,93,96,104,107,109,110] and superoxide dismutase (SOD) levels,[92,93,104,107,109,111] a decrease or attenuation in lipid peroxidation,[93,103,104,108−110] the prevention of neuronal TH^+ decrease,[87,91,92,94,103,104,108,111,115] an increase in dopamine levels,[90−94,111,113] and an improvement of locomotor skills.[86,87,90−94,96,104,105,107,108,111,112,115]

The studies that investigated the pharmacokinetic properties of the phytomedicine compared to the phyto-nanomedicine were able to show that NPs improved the pharmacokinetic parameters of the phytochemical.[86−88,90,91,93,102,109] More specifically, these studies were able to show that utilization of NPs increased the extent of exposure and the elimination of the phytomedicine in the brain.[86−88,90,91,93,102,109] Those studies that functionalized the NPs primarily did so with the use of P188,[91,114] PS80,[88,103] lactoferrin,[92,94] and lactoferrin with NIR.[93] The use of lactoferrin showed 1-[94] and 25-fold increases[92] compared to the control and 2-[94] and 3-fold increases[92] compared to the NPs not functionalized with lactoferrin. Moreover, the use of NIR show a 2-fold increase compared to the control and a 3-fold increase compared to NPs not functionalized with NIR and lactoferrin.[93] Although the studies that functionalized NPs with P188 or PS80 did not compare the efficiency of these surfactants to the controls, they were able to indicate neuroprotective effects, thereby implying that these NPs were able to cross the BBB.

4.3. Effects of Phytochemicals on Disease Processes Implicit in PD. The main pathophysiological hallmark of PD is the progressive death of dopaminergic neurons in the substantia nigra pars compacta, which eventually spreads throughout the brain in the later stages of the disease.[117−120] Several molecular mechanisms have been linked to this degeneration, including the aggregation of α-synuclein, oxidative stress, lipid peroxidation, inflammation, and mitochondrial dysfunction.[121] However, studies on PD are limited by the model used, as not all models are able to display all the pathobiological features of this disorder. One of the studies discussed here showed that the MPP^+ toxin was able to induce a decrease in cell viability, antioxidant activity, lipid peroxidation, and mitochondrial dysfunction.[85] Notably, the phytomedicines discussed in this Review were shown to target one or more of these mechanisms. Phytomedicines that demonstrated possible neuroprotective effects include turmeric/curcumin,[85,88] schisantherin A,[86,87] naringenin,[95] puerarin,[89] paeonifliorin,[93] glinkogide B,[90,91] resveratrol,[94,109] epigallocatechin gallate,[115] *Bacopa monnieri*,[107] and fisetin.[116] The neuroprotective effects examined in these studies include

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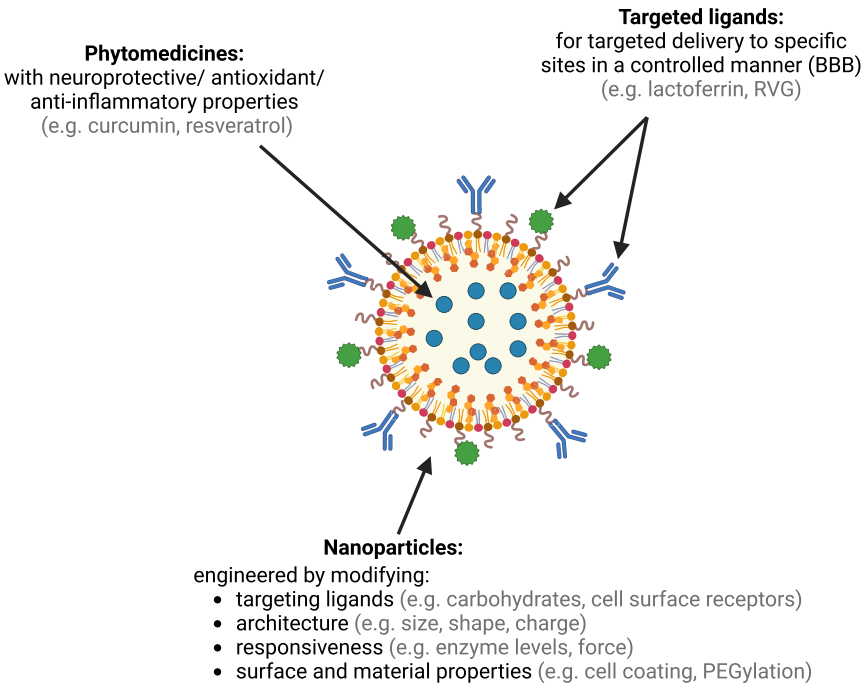

Figure 1. Targeted drug delivery nanophytomedicine approaches for Parkinson's disease Abbreviations: BBB, blood-brain barrier; RVG, rabies virus glycoprotein

increased cell viability, ATP levels, and cell survival pathways, as well as a decrease in apoptosis and necrosis. Oxidative stress was attenuated by turmeric/curcumin,[85,112] resveratrol,[94,108,109] hypericum hookerianum,[113] puerarin,[92,102] paeoniflorin,[93] lutein,[111] pueperine,[104] and *Bacopa monnieri*.[107] Lipid peroxidation, a consequence of oxidative stress, was shown to be improved by turmeric/curcumin,[85] resveratrol,[103,108] paeoniflorin,[93] and puerarin.[92] Mitochondrial dysfunction was improved by turmeric/curcumin,[85,112] puerarin,[89] glinkogide B,[90] and resveratrol.[94,108] Inflammation levels were improved following the use of curcumin[96] and resveratrol,[94] while α-synuclein aggregation was decreased by curcumin[88,96] and epigallocatechin gallate.[115] Tyrosine hydroxylase and dopamine levels were increased by curcumin,[99] resveratrol,[103] hypericum hookerianum,[113] schisantherin A,[87] epigallocatechin gallate,[115] paeoniflorin,[93] glinkogide B,[90,91] lutein,[111] puerarin,[92] pueperine,[104] and fitesin.[107] Finally, motor symptoms in animal models were improved by fisetin,[107] *Bacopa monnieri*,[107] resveratrol,[94] pueperine,[104] puerarine,[92] curcumin,[112,122] lutein,[111] glinkogide B,[90,91] paeoniflorin,[93] and schisantherin A.[86,87]

4.4. Overall Summary of Findings. In summary, all of the *in vitro* and *in vivo* studies summarized in Tables 1 and 2 provide clear evidence that NPs are promising drug delivery agents that not only improve the efficacy of the phytomedicines but can also help improve their BBB permeability. In addition, the functionalization of these nanoparticles can further improve the effects of phytomedicines and provide a targeted effect. These studies also show the neuroprotective effects of phytochemicals, with curcumin and resveratrol being able to improve several molecular features of PD, including oxidative stress, lipid peroxidase, mitochondrial dysfunction, and motor symptoms. However, it should be cautioned that these overall promising findings may be due to publication bias. Furthermore, a limitation of previous research is that while there is evidence supporting the possible therapeutic effects of nanophytomedicines in PD *in vivo* and *in vitro* studies, studies involving *ex vivo* models are absent. Future studies should, therefore, focus on *ex vivo* models taken from people with PD. This will better reflect the genomic background of the individual with PD and will serve as a model developed from both environmental and genetic factors to investigate the effects of nanophytomedicines as a potential therapeutic agent for PD.

5. FUTURE DIRECTIONS FOR NANO-PHYTOMEDICINE

The summaries above highlight the advantages of using current nanophytomedicines, which show great promise. These nanophytomedicines can be grouped into three main categories based on the NP mode of action: drug delivery carriers, device-assisted drug delivery, and targeted drug delivery. As the name suggests, the majority of the research to date falls within the drug delivery carrier category. The device-assisted drug delivery group makes use of laser irradiation (NIR) or ultrasound to enhance the efficacy of the nanophytomedicines. The last category, targeted drug delivery, falls in the precision medicine umbrella, using ligands such as lactoferrin and rabies virus glycoprotein to ensure the phytomedicine is delivered across the BBB. While the two latter modes of action enhance the efficacy of the nanophytomedicines, targeted nanoparticles provide an eloquent solution, directing their phytomedicines to the desired location where they release the required dose.

Targeted drug delivery is one of the leading candidates in medical sciences due to the almost infinite number of permutations that can be engineered by modifying properties such as architecture, targeting ligands, responsiveness, and surface and material properties for the purpose of diagnosis or treatment.[123] Some of these targeted drug delivery approaches for nanophytomedicines for PD are summarized in Figure 1. Given the immense number of medicinal plants and rapid

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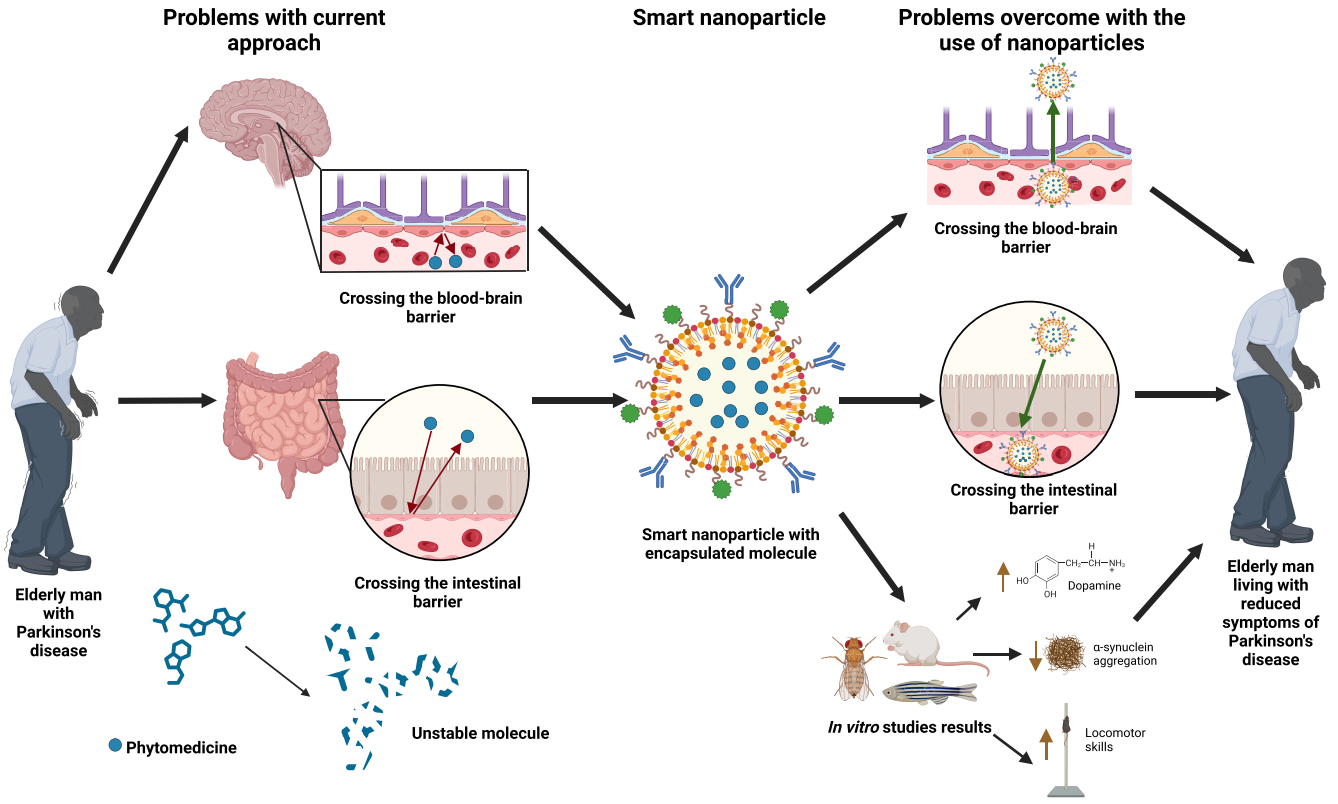

Figure 2. Limitations of the use of phytomedicines for the treatment of Parkinson's disease, which can be overcome using smart nanoparticles

advancement in nanoparticle technology and knowledge, research into nanophytomedicine for PD holds promise. It must, however, be mentioned that there are some challenges when facing the development of nanophytomedicines for the treatment of diseases, including PD. While there are positive preclinical results of nanophytomedicines,[30−32] clinical translation has not progressed at the same extent despite the therapeutic advantages of these nanomedicines.[124] Clinical translation of nanomedicines is a costly and time-consuming process due to the complexity of nanomedicine technology compared to conventional formulation technology containing free drug in suitable dosage forms (e.g., injections, tablets, and capsules).[125] The key issues related to clinical development of nanomedicines in comparison to current therapies include biological challenges, large-scale manufacturing, biocompatibility and safety, intellectual property, and overall cost-effectiveness.[124] These key issues, however, can be overcome with careful planning to reduce the complexity of the design of the nanomedicine, providing attention to the stability following *in vivo* administration with high control over the physiochemical properties of the nanomedicine (e.g., size and polydispersity index, morphology, drug encapsulation efficiency, and charge), as well as utilizing biocompatible, nontoxic, and biodegradable compounds for the composition of the nanoplatform.[124,125]

6. CONCLUSION

Phytomedicine has been demonstrated as a promising preventative or therapeutic candidate for the treatment of PD due to its involvement in several neuroprotective pathways and its good safety profile.[126] Although these properties have been well established, the use of phytomedicines as therapeutic agents for PD is restricted due to their poor pharmacokinetic properties. However, with the use of nanomedicine, these poor pharmacokinetic properties of drugs, including phytomedicines, can be overcome, as illustrated in Figure 2. Previous *in vitro* studies (Table 1) not only showed that nanoparticles improved the effects of phytomedicines but also improved their BBB permeability, which was further enhanced by the functionalization of these nanoparticles. The *in vivo* studies (Table 2) confirmed these findings, which also demonstrated promising neuroprotective effects of nanophytomedicines, including alleviation of motor symptoms, in mice, rats, zebrafish, and *Drosophila melanogaster*. These studies, however, focused on neurotoxin-treated models, which only provided a representation of environmental factors and thus did not take genetic factors that may lead to the development of PD into consideration. In addition, research using *ex vivo* models is limited, and inclusion of these studies will thus further enhance the understanding of nanophytomedicines and their effects on PD pathobiology.

In summary, the use of nanophytomedicines for the treatment of PD is a promising field but requires more research before it can progress to clinical trials. Future engineering of smart nanoparticle drug delivery systems should focus on more efficient and targeted drug delivery, which is the holy grail of drug delivery systems. It is critical to maximize the efficacy of the therapeutic drug at the target site/organ and to minimize the drug's side effects by performing pharmacokinetic studies,[34] controlling its biodistribution, and preventing its release at nontarget sites.[127]

While human studies investigating nanophytomedicines are limited, *in vivo* studies in animal models have shown promising results in reducing PD-related processes, revealing that they could be used as therapeutic agents for the treatment of PD in the future.

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Author Contributions

[±]Joint first authors. S.B. and A.D. conceptualized the manuscript. J.B. performed the literature searches (assisted by S.D.). J.B. and A.B. wrote the first draft of the manuscript, compiled the tables, and prepared Figure 2. S.D., A.D., and S.B. wrote sections of the manuscript. S.D. prepared Figure 1. All authors reviewed, edited and approved the final version of the manuscript for submission.

Notes

The authors declare no competing financial interest.

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