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Utilizing secretomes as a novel molecular-based therapy for Parkinson's disease: A scoping review

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ABSTRACT

Parkinson's disease (PD) is a neurodegenerative disorder that affects multiple body systems and results in a variety of motor and non-motor symptoms. Recent research has highlighted the importance of secretome, a diverse array of bioactive molecules produced by mesenchymal stem cells (MSCs). This study explores the progress and potential benefits of secretome use in treating PD. A scoping review was conducted following the Preferred Reporting Items for Scoping Reviews protocol, utilizing journals from PubMed Central, ScienceDirect, and Scopus databases with no time restrictions. The findings suggest that secretome shows promise in developing new therapies for PD, particularly due to its superior antioxidant, neuroprotective, and neurodifferentiation effects on dopaminergic neurons compared to MSCs. These effects have been linked to notable improvements in motor, behavioral, and morphological changes. However, for secretome therapy to be effectively implemented in human patients with PD, factors such as production stages, release mechanisms, and administration routes require further investigation.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder that affects multiple body systems and leads to a wide range of motor and non-motor symptoms. These symptoms arise from significant disturbances in the neurotransmitter system, particularly in the dopamine system. In PD, there is a notable loss of neurons in specific regions of the brain, such as the substantia nigra pars compacta (SNpc). This neuronal loss results in a deficiency of dopamine in another brain region known as the striatum, which plays a crucial role in motor control [1–3].

Moreover, PD is characterized by the presence of abnormal structures within cells, specifically the accumulation of protein aggregates containing α-synuclein. These intracellular inclusions are considered primary neuropathological hallmarks of PD. The combination of dopamine deficiency in the striatum and the presence of α-synuclein aggregates in neurons contributes to the development of motor symptoms and other manifestations observed in individuals with PD [1–3].

Based on information from the World Health Organization, as of 2019, approximately 8.5 million people are living with PD, with 5.8 million of these individuals experiencing disability. Additionally, the mortality rate associated with the disease reached 329 thousand, which represents an increase of more than 100% compared to data from 2000 [4]. According to the Parkinson Foundation, although Parkinson's is more common in older populations, an estimated 4% of all cases are diagnosed in individuals under the age of 50. This has a

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significant impact, especially on patients who are still in their productive years [5].

The treatment of PD primarily focuses on addressing dopamine deficiency in the brain through dopamine replacement therapy, which involves administering medications to supplement dopamine levels and alleviate motor symptoms. Non-dopaminergic strategies are also important for managing symptoms that are not directly related to dopamine deficiency and for improving overall quality of life. Deep brain stimulation is an option for individuals with motor complications or levodopa-related fluctuations, where electrodes are implanted in the brain to modulate activity and control symptoms while reducing medication side effects [6–9].

Current treatment approaches for PD can lead to clinical improvements in some individuals. However, they often carry the risk of consequential complications and are only effective for a limited time in a subset of patients. Additionally, these treatments do not address the underlying neuropathological processes that result in progressive cell death in patients with PD. This limitation highlights the need for alternative therapeutic strategies that target the root cause of the disease and provide long-term benefits [10,11].

Mesenchymal stem cell (MSC)-based approaches have been identified as potentially effective therapeutic alternatives for neurodegenerative conditions, such as PD. MSCs possess unique characteristics that make them attractive candidates for use in regenerative medicine. These cells can differentiate into various cell types and secrete bioactive molecules that promote tissue repair and regeneration, modulate immune responses, and exhibit anti-inflammatory properties. By harnessing these inherent qualities, MSC-based therapies offer a novel approach to alleviate symptoms and potentially modify disease progression by addressing the mechanisms underlying neurodegeneration in PD [12–15].

Initially, the therapeutic benefits of MSCs in PD were thought to stem from their ability to engraft into damaged tissues and differentiate into various cell types, including dopaminergic neurons. However, recent research has shown that the long-term survival of implanted MSCs is limited and that their therapeutic effects are primarily mediated by their paracrine activity rather than by their ability to directly replace damaged cells [16,17].

Paracrine activity refers to the release of bioactive molecules such as growth factors, cytokines, and extracellular vesicles by MSCs into the surrounding environment. These secretory factors play a crucial role in modulating the cellular microenvironment, promoting tissue repair, reducing inflammation, and supporting cell survival and regeneration. This paracrine mechanism allows MSCs to indirectly exert their therapeutic effects by influencing neighboring cells and tissues [16–19].

Recent research has highlighted the significance of the secretome, which refers to the diverse collection of physiologically active compounds secreted by MSCs. These bioactive molecules include growth factors, cytokines, extracellular vesicles, and other signaling molecules that collectively play crucial roles in mediating the therapeutic effects of MSCs. Studies have shown that secretome-derived products from MSCs possess neuroregulatory properties that can influence key pathological processes associated with maintaining cellular balance and function, including cellular differentiation and proliferation, blood vessel formation and regeneration, inflammatory processes, and regulation of oxidative stress [16,20–22].

Research related to the use of secretomes for the treatment of neurodegenerative diseases in recent years has advanced. However, there are still many differences among the various studies conducted such as the type of initial stem cell used as a source of secretome, the experimental animals used, and the method of secretome production. Previous reviews discussing the use of secretome in neurodegenerative diseases have been published before, but they did not focus on PD specifically [22,23,24]. In addition, the existing reviews are primarily narrative in nature. In this new review, the scoping review method was utilized to cover a wide range of studies and provide comprehensive information from the existing studies on the use of the secretome in PD.

Therefore, this study aims to determine the various utilizations of the secretome from existing studies in PD cases, how the secretome provides benefits for the treatment of these diseases, and the molecular mechanisms underlying these effects, as well as the latest developments related to secretome research in PD.

METHODS

Study design

This was a scoping review based on the Preferred Reporting Items for Scoping Reviews protocol (PRISMA-ScR). The assessment results of the checklist-based writing adequacy of the PRISMA-ScR are shown in Supplementary Table 1. This scoping review aimed to determine the development of secretome use in PD therapy, particularly regarding the updates

Table 1. Eligibility criteria.

Eligibility criteria	Inclusion criteria	Exclusion criteria
Study type	Experimental study	Case report, Case series, Research protocol, Observational atudies, and Review article
Publication Type	Scientific published journal	Conference abstracts, Chapter book
Language	English	–
Year range	No year restriction of published journal	–
Data collection	Primary research	–
Study population	Human with Parkinson disease or animal or cell culture of Parkinson disease model	–
Concept	Molecular based therapy	–
Context	Usage of secretome for Parkinson disease	–

in research and the molecular mechanisms associated with the effects of secretome on the repair or prevention of cell degeneration in PD.

Eligibility criteria

The eligibility criteria for the journals included in this study encompass several assessments, with the inclusion and exclusion criteria outlined in Table 1. In this study, there were no time limitations for the included journals, allowing for more comprehensive results. This scoping review will also focus on the utilization of molecular therapy in the management of PD, particularly regarding the use of secretome as a novel therapeutic approach.

Search strategy

The journals used for this study were obtained from the PubMed Central, ScienceDirect, and Scopus databases. The search covered journals from their inception until March 27, 2024. The keywords for this study included "Parkinson," "Secretome," "Exosome," "therapy," and "treatment." A more detailed search strategy for this review is provided in Supplementary Table 2.

Study selection

Two authors independently reviewed the abstracts, followed by a full-text assessment of the studies that met the inclusion criteria. Any discrepancies were resolved through discussion. The inclusion criteria were based on the population, concept, and context framework, specifically focusing on studies related to PD or PD models, the use of secretome as an intervention, and the examination of the molecular therapies underlying the outcomes

Data extraction

The journals obtained from the full-text analysis will be utilized in the data extraction process. The results of the data extraction will include information on the first author, year of publication, country where the study was conducted, study design, study population, study objectives, route of secretome administration, outcomes of the study, and the molecular mechanisms underlying the results.

RESULTS

Based on the screening results, 15 journals (Fig. 1) were included in this study. All included studies were conducted either *in vitro* or *in vivo*. No human studies related to the use of the secretome in the management of PD were found during the search. Most studies on the use of the secretome were conducted in Portugal ($n = 9$), followed by China ($n = 2$). In other countries, such as Italy, Sweden, India, and the Republic of Korea, only one study per country was conducted. In *in vivo* studies, most models utilized mice, although some studies also employed *Caenorhabditis elegans* models. A complete summary of the studies included in this review is presented in Table 2. Several sources of the secretome used in the studies were identified, and various routes of secretome administration were observed. The types of secretome sources and administration routes are listed in Table 3.

DISCUSSION

Secretome characteristics and molecular effect

An *in vitro* study using the secretome of hBM-MSCs applied to hNPCs demonstrated that progenitor cells were transformed into mature cells (MAP-2-positive) and immature neurons (DCX-positive). When comparing the effects of the whole secretome and its vesicular fraction to those of the protein fraction, it was observed that both the secretome and its vesicular fraction induced a higher differentiation rate of hNPCs than the protein fraction alone [25].

BDNF, NGF, and VEGF were found to be produced by MSCs in the conditioned media [26]. Additionally, other cell types, such as secretome-producing pericytes, exhibited increased production of pro-regenerative molecules following stimulation with PDGF-BB, which binds to the PDGFRβ receptor [27,28]. An *in vitro* study of parkinsonism using LUHMES, a type of human-derived cell culture, demonstrated that PDGF-BB-treated pericytes ($C^{MPDGFBB}$) resulted in a significant increase in markers of DA neurons, specifically TH and Dopa-β-H, compared to LUHMES that received PDGF-BB alone [29–32].

In an *in vivo* study using *C. elegans* to assess the effects of the secretome from hBMSCs on a model with α-syn overexpression, it was found that secretome administration helped maintain a higher percentage of DA neurons in the study subjects compared to the controls, with results of 44%–10%, respectively. The secretome primarily exerted neuroprotective effects on neurons in the anterior deirid and cephalic regions. Additionally, the *C. elegans* group treated with the secretome exhibited a 13% reduction in α-syn inclusion bodies compared to the control group [33].

Another study utilized a novel *in vitro* model based on 6-OHDA-induced neurotoxicity in hMOs, which allowed for three-dimensional mask and skeleton analysis to examine the complexity of DA neurons. The results indicated that treatment with the secretome led to significantly less neurite fragmentation compared to the untreated group, suggesting a protective effect on the DA neuronal network [34].

The secretome contains several proteins that can enhance function and strengthen the connections between dopaminergic DA neurons in the nigrostriatal region. Notably, various components of the secretome exhibit anti-proteotoxic effects against α-syn, including BDNF, CFL1, CLU, CST3, HSPA8, HSPB1, IGF1, LGALS1, MMP2, DJ-1 or PARK7, UBE3A, UCHL1, and VEGFB [33,35–38].

The use of the secretome has also revealed molecular effects associated with the apoptotic process in cells. Analysis indicated an increase in the expression of BCL-2 and a decrease in CASP3 [26,39]. Furthermore, the secretome demonstrated a modulating effect on the differentiation of neuronal cells into dopaminergic neurons, particularly in the context of PD. This effect is linked to the Dickkopf 3 molecule, which influences the Wnt/β-catenin signaling pathway [40,41].

Effect of secretome on mitochondrial function

Impaired mitochondrial function is associated with the pathogenesis of PD. Patients with PD exhibit impaired

Table 2. Summary of included studies.

First Author, year	Country	Study design	Population	Objective
Chierchia *et al.* [98]	Italy	*In vitro* study	Neuroblastoma SH-SY5Y cells PD model induced by toxin 6-hydroxydopamine	Examine the protective effects of the secretome derived from hydrogel-embedded adipose mesenchymal stem cells against the toxin 6-hydroxydopamine associated with PD
Gaceb *et al.* [32]	Sweden	*In vitro* study	Dopaminergic neurons obtained from the LUHMES cell line, exposed to MPP+ and 6-OHDA to induce PD	Create an *in vitro* partial lesion model of dopaminergic neurons to investigate the effects of various molecules on their neuroprotective or neurorestorative potential regarding the dopaminergic phenotype
Marques *et al.* [71]	Portugal	*In vitro* and *In vivo* study	hNPCs and dopaminergic neurons that overexpress α-synuclein in a Caenorhabditis elegans model	Examine the neurodifferentiation and neuroprotective potential of secretome derived from mesenchymal stromal cells produced in various dynamic systems, especially in relation to PD
Marques *et al.* [92]	Portugal	*In vivo* study	Rat model utilizing a viral vector to overexpress A53T-α-synuclein	Assess the effects of the secretome derived from bone marrow mesenchymal stromal cells on α-synuclein overexpression in a rat model of PD, aiming to develop a potential therapy for this neurodegenerative disorder
Marques *et al.* [33]	Portugal	*In vitro* and *In vivo* study	Alpha-synuclein overexpression model in the dopamine neurons and body wall muscle cells of the *C. elegans*	Explore the potential neuroprotective effects of human BMSC secretome in preventing the degeneration of dopaminergic neurons and reducing α-synuclein inclusions in models of PD
Mahendru *et al.* [26]	India	*In vivo* study	Male Wistar rats PD model with administration of 6-OHDA unilaterally	Examine the effects of the secretome from human mesenchymal stem cells on brain structure and animal behavior in a rat model of PD
Mendes-Pinheiro *et al.* [40]	Portugal	*In vivo* study	PD rats model induced by 6-OHDA injections	Evaluate the histological and motor improvements induced by the secretome of undifferentiated neural progenitor cells in a rat model of PD
Mendes-Pinheiro *et al.* [91]	Portugal	*In vivo* study	PD rats model induced by 6-OHDA injections into the MFB	Investigate the neuroprotective effects of BMSC secretome in a PD rat model
Mendes-Pinheiro *et al.* [34]	Portugal	*In vivo*	Unilateral intrastriatal 6-OHDA PD mouse model and human midbrain-specific organoids for *in vitro* model	Explore the potential of human BMSC secretome as a treatment for PD
Ni *et al.* [48]	China	*In vivo* and *in vitro*	8-week-old male SD rats with unilateral stereotactic brain injection of 40 mM 6-OHDA into the left MFB of the rats for *in vivo* model. PC12 cell-damaged model used for *in vitro* model	Investigate the potential therapeutic effects of neural stem cell secretome, specifically NSC-CM, on improving motor and non-motor deficits in a PD rat model, as well as its protective effects on damaged neurons through mechanisms such as reducing oxidative stress and improving mitochondrial dysfunction
Ramalingam *et al.* [60]	Republic of Korea	*In vitro* study	SH-SY5Y cells induced by ROT, a mitochondrial complex I inhibitor that reproduces α-synuclein aggregation seen in PD	Examine the neuroprotective effects of the secretome from neural-induced adipose-derived stem cells in mitigating ROT-induced toxicity in SH-SY5Y cells
Teixeira *et al.* [81]	Portugal	*In vivo* study	Male Wistar rats. The rats were induced with 6-OHDA to create a model of PD	Evaluate the therapeutic potential of the secretome of human mesenchymal stem cells in reversing the Parkinsonian phenotype and promoting the recovery of dopaminergic neurons in a rat model of PD
Teixeira *et al.* [81]	Portugal	*In vivo* study	Rats that were injected with 6-OHDA unilateral injection into the MFB to induce model of PD	assess the impact of hBM-MSCs secretome in a 6-OHDA PD model compared to levodopa administration by evaluating animals' motor performance and histological parameters in the SN and STR
Vilaça-Faria *et al.* [25]	Portugal	*In vivo* study	Rat with involved unilateral injection of 6-OHDA in the MFB of the animals to induce PD	Investigate the potential therapeutic effects of fractionating stem cells secretome for PD
Yao *et al.* [82]	China	*In vivo* study	PD model rats by injecting 6-OHDA into the VTA and MFB of the rat	Investigate the potential of combined treatment with MSC-secreted factors and neural stem cell transplantation in promoting functional recovery in PD rats

LUHMES: Lung human mesencephalic; MMP+: 1-methyl-4-phenylpyridinium; 6-OHDA, 6-hydroxydopamine; hNPCs, human neural progenitor cells; PD, Parkinson's disease; BMSC, bone marrow-derived mesenchymal stem cell; MFB, medial forebrain bundle; NSC-CM, neural stem cell-conditioned medium; SD, Sprague-Dawley; h-BM-MSCs, human bone marrow mesenchymal stem cells; SN, substantia nigra; STR, striatum; VTA, ventral tegmental area; MSC, mesenchymal.

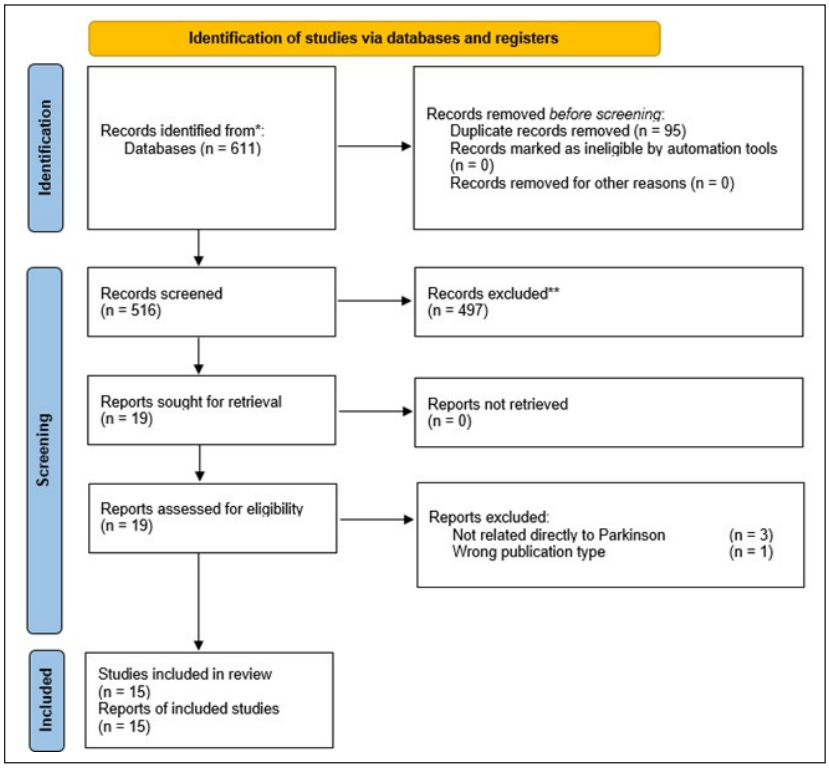

Figure 1. PRISMA-ScR flow diagram of study selection.

mitochondrial biosynthesis, which is related mtDNA replication and transcription. This disruption affects the mitochondrial ETC, resulting in the accumulation of free radicals [42,43]. Under normal circumstances, mitochondria can counteract the accumulation of reactive oxygen species (ROS); however, this function is compromised when the structure and function of the mitochondria are impaired. Additionally, mitochondrial dysfunction triggers the import of α-synuclein into the mitochondria. The accumulation of α-synuclein in mitochondria contributes to mitochondrial damage, creating a detrimental cycle that exacerbates mitochondrial dysfunction and cellular damage in PD [44–46].

The use of secretome has been shown to reduce mitochondrial energy generation, mitochondrial membrane potential, and mitochondrial mass in PD cells. By preserving some of these mitochondrial parameters, the secretome can mitigate the effects of oxidative stress and apoptosis that play a role in the development of PD [47]. Important molecules involved in this process include PARK7 and Sirt1 [48]. The PARK7 protein, also known as DJ-1, functions as a cellular oxidative stress sensor and plays a crucial role in maintaining cellular homeostasis [49]. PARK7 has several protective functions, including inhibiting the accumulation of glycosylated α-synuclein, increasing the expression of antioxidant enzymes to reduce ROS production, and enhancing ATP production in dopaminergic neurons [50–53]. Furthermore, studies have established a connection between PARK7 and Sirt1.

Research indicates that PARK7 can directly bind to and activate Sirt1, leading to the inhibition of p53 acetylation and a reduction in cell apoptosis [54,55]. One study demonstrated that Sirt1 levels were upregulated following exogenous recombinant PARK7 treatment, although this finding remains preliminary [48]. Sirt1, a member of the sirtuin family of proteins, plays a crucial role in regulating various physiological processes, particularly in the mitochondria. It is a NAD+-dependent lysine deacetylase that is abundant in the brain [47]. Sirt1 is closely linked to mitochondrial function, as it promotes mitochondrial biogenesis and energy synthesis by activating transcription factors such as p53, CREB, PGC-1α, and HIF-1α. Additionally, Sirt1 is involved in inhibiting oxidative stress and facilitating the degradation of α-synuclein oligomers, which have been implicated in PD pathology [56,57].

In a study utilizing rotenone (ROT) a molecule that functions as a mitochondrial complex I inhibitor and causes an increase in α-synuclein, the protective effect of secretomes produced by NI-ADSC-SM was observed [58–60]. The protective effect of the NI-ADSC-SM secretome was found to be superior to that of human ADSC-SM in general [60]. Cells treated with ROT exhibited an increase in calcium levels, which can affect the incidence of cell damage [60,61]. The secretome of NI-ADSC-SM showed a decrease in calcium levels compared to the secretome of ADSC-SM [60].

In examining the protein expression of LRRK2, PINK1, parkin, soluble and insoluble Ub proteins, DJ-1, and TOM20, it was found that NI-ADSC-SM secretome administration decreased the expression of LRRK2 and insoluble Ub proteins, which play a role in the progression of PD [60,62]. For the expression of parkin, soluble Ub protein, DJ-1, and TOM20,

Table 3. Details of secretome therapy and administration.

First Author, year	Source of secretome	Secretome administration
Chierchia *et al.* [98]	RAA-MSCs	Secretome from RAA-MSCs was administered to the study participant by pre-conditioning neuroblastoma SH-SY5Y cells with the CM from RAA-MSCs for 24 hours before exposing the cells to oxidative stress inducers such as H2O2 or the dopaminergic-selective toxin 6-OHDA
Gaceb *et al.* [32]	Human brain-derived pericytes stimulated with PDGF-BB	Secretome extracted from human brain-derived pericytes stimulated with PDGF-BB was administered to the study participants by incubating the differentiated LUHMES cells with CM_PDGFBB
Marques *et al.* [71]	Human BMSCs that were isolated from bone marrow aspirates obtained from healthy donors	Secretome produced by BMSCs was collected from cells expanded in a SP and in a VWBR system. The secretome was then used to induce neurodifferentiation of hNPCs and to prevent dopaminergic neuron degeneration in a Caenorhabditis elegans model of PD
Marques *et al.* [92]	Bone marrow-derived MSCs that were cultured until reaching the stationary cell growth phase	Secretome administered via bilateral injections. The animals were anesthetized and placed on a stereotaxic frame, and the secretome was injected bilaterally into specific coordinates in the SN and STR using a needle. The injection volume was 24 ml of 100x concentrated secretome, with 4 ml delivered in the SN and at each coordinate in the STR for both hemispheres. The injection rate was 1 ml/minute, and the needle was left in place for 4 minutes after each injection to prevent backflow
Marques *et al.* [33]	hBMSCs	The secretome was administered to the Caenorhabditis elegans models of PD by incorporating it into the animals' food source. Two types of plates were prepared: one seeded with the concentrated secretome diluted in inactivated Escherichia coli OP50 (final concentration = 1x)
Mahendru *et al.* [26]	The secretome used in the study was derived from MSCs isolated from the bone marrow of 3-month-old male Wistar rats	The secretome derived from BM-MSCs was administered intravenously to the rats in the 6-OHDA model of PD. The secretome was given as an intravenous injection, which is a non-invasive method of administration compared to direct intracranial injection
Mendes-Pinheiro *et al.* [40]	hNPCs that were cultured and grown using conditioned media	The secretome extracted from hNPCs was administered by injection directly into the SNpc and into specific coordinates in the striatum of the rats
Mendes-Pinheiro *et al.* [94]	hBMSCs cultured form conditioned media	The hBMSCs secretome was injected into the study participants. The injections were targeted at the SNpc and the striatum. The secretome was injected into four different sites within these brain regions
Mendes-Pinheiro *et al.* [34]	The secretome used in this study was collected from BM-MSCs that were cultured and expanded in specific growth media	Secretome derived from BM-MSCs was administered to the study participants using two different routes: IC injections and intravenous IV injections. The effects of these two administration routes were compared to evaluate their impact on motor function recovery and dopaminergic loss protection in the context of PD treatment. The results indicated that multiple systemic IV injections resulted in larger therapeutic effects compared to IC injection
Ni *et al.* [48]	The secretome used in this study was extracted from hESC-NSCs. These NSCs were cultured in specific media conditions, and the conditioned medium was collected when the NSCs reached about 90% confluence	The secretome, specifically the NSC-CM, was administered by injection into the STR and SN of the PD rat model. The NSC-CM was concentrated 10 times using a freeze dryer before being injected into the brain regions of interest

RAA-MSCs: rat adipose tissue-derived mesenchymal stem cells; CM: conditioned medium; H2O2: hydrogen peroxide; 6-OHDA: 6-hydroxydopamine; PDGF-BB: platelet-derived growth factor BB; LUHMES: Lund human mesencephalic; CM_PDGFBB: conditioned medium from PDGF-BB-treated pericytes; BMSCs: bone marrow mesenchymal stromal cells; SP: spinner flask; VWBR: Vertical-Wheel ™ bioreactor; hNPCs: human neural progenitor cells; PD: Parkinson disease; MSCs: mesenchymal stromal cells; SN: substantia nigra; STR: striatum; hBMSCs: human bone marrow-derived mesenchymal stem cells; MSCs: mesenchymal stem cells; BM-MSCs: bone marrow mesenchymal stem cells; SNpc: substantia nigra pars compacta; BM-MSCs: bone marrow-derived mesenchymal stem cells; IC: intracerebral; IV: intravenous; hESC-NSCs: human embryonic stem cell-derived neural stem cells; NSC-CM: neural stem cell-conditioned medium.

an increase in expression was observed, although no increase in PINK1 expression was noted [60].

PINK1 and parkin are essential for mitophagy, targeting damaged mitochondria for degradation. Decreased levels of PINK1 and parkin induced by ROT exposure led to increased mitochondrial fragmentation, potentially resulting in apoptotic cell death due to ROS-induced stress [60,63–65]. The activation of mitophagy aims to clear ubiquitinated substrates, such as misfolded α-synuclein protein aggregates, for cellular clearance [59]. ROT exposure also decreased soluble Ub levels while increasing insoluble Ub levels in cell lysates [60]. This accumulation of Ub conjugates under oxidative stress may lead to the aggregation of misfolded proteins, which are targeted for degradation through mitophagy mechanisms [60,66].

Decreased levels of DJ-1, a protein crucial for mitigating α-synuclein aggregation and maintaining the mitochondrial function, after ROT exposure, may be linked to increased ROS production, promoting α-synuclein aggregation and mitochondrial dysfunction [60,67]. ROT exposure also decreased TOM20 levels, a protein involved in mitochondrial protein import and function, potentially impairing mitochondrial function. The modulation of TOM20 and DJ-1 levels by NI-ADSC-SM treatment may contribute to improved mitochondrial function, counteract α-synuclein aggregation, and enhance overall neuronal health in the context of PD-associated pathologies [60,68].

Effect of dynamic system in secretome production

Research is currently exploring the use of system dynamics for the large-scale production of secretomes, particularly through bioreactor systems. These systems can significantly influence the molecular expression of secretomes compared to static culture models [36,69–71]. A study compared two dynamic models, specifically the SP and VWBR, using two different culture media: AlphaMEM for SP1 and VWBR1, and Neurobasal-A for SP2 and VWBR2 [71]. Each model operates with distinct mechanisms and agitation speeds [72].

The results from the bioreactor experiments indicated fold expansion rates of 4.19 times for VWBR1, 2.93 times for SP1, 2.58 times for VWBR2, and 2.45 times for SP2. The doubling times were 2.24 days for VWBR1, 1.92 days for SP1, 2.90 days for VWBR2, and 2.23 days for SP2. Cells cultured in the dynamic bioreactor system maintained their MSC phenotype and multilineage differentiation capabilities, along with the ability to induce neurodifferentiation. However, the secretomes produced from these dynamic systems exhibited varying neuroprotective effects, with those from the SP model showing superior neuroprotective properties compared to those from VWBR. This variation is attributed to the different secretory profiles generated by the secretomes in the distinct dynamic models and culture conditions. Notably, secretome from SP1 demonstrated a higher secretory intensity overall, with MCP-1 and IL-8 being highly expressed across all secretome types. In contrast, higher levels of TNF-β, MMP3, and IL-6 were observed in SP, while VWBR1 showed increased osteopontin expression, and VWBR2 had higher levels of HB-EGF, GCSF, NGFβ, and IL-13 [71].

The differences in neuroprotective effects may be linked to the shear stress experienced in the two bioreactor types, with SP exhibiting higher shear stress levels [72–74]. Additionally, the glucose concentration was lower in SP (3.4 ± 1.1 mM) compared to VWBR (9.5 ± 3.4 mM) [71]. This suggests that higher stress conditions may enhance the secretory production of the secretome, particularly concerning cytokines with anti-inflammatory properties, such as oncostatin M, TGF-β1, IL-4, and IL-6 [71,75–80]. However, the precise effects of stress on these outcomes remain largely unexplored.

Effect of secretome on behavioral and motor parameters

In studies involving PD models treated with secretome, various behavioral and motor function tests have been employed, including rotational behavior, the MWM, rotarod, staircase, motor swimming, beam balance walk, and pole tests. Results indicate that animals receiving secretome therapy generally performed better than those treated with other therapies, such as levodopa or hNPC transplantation alone [25,26,34,40,81,82].

Notably, in experiments where a combination of NSC transplantation and secretome therapy was administered, significant motor improvements were observed. In contrast, the group receiving only transplantation did not show enhancements in motor coordination or fine motor skills in the rotarod and staircase tests compared to the untreated group. This suggests that combining transplantation with secretome therapy is more effective for recovering motor function and cognitive abilities in PD model rats [40,82]. Furthermore, another study reported that animals treated with the secretome derived from hBM-MSCs exhibited significant improvements in motor functionality, as evidenced by an increased success rate in retrieving food pellets on the affected side [25].

The route of secretome administration also plays a crucial role in the outcomes of motor and behavioral functions. Research has shown that IV administration yields better results than IC administration [34].

It is essential to note that while the rotarod test evaluates motor coordination, it does not specifically assess manipulation skills involving individual paws, which is a focus of the staircase test. The staircase test is designed to provide a more precise evaluation of performance, as its configuration prevents animals from compensating by using their unaffected paw, even when the affected side is presumed to be impaired. This distinction is not captured by the rotarod test [83,84].

Effect of secretome in pro-inflammatory cytokine levels

The administration of secretome in PD models has demonstrated several beneficial effects on oxidative stress and inflammation. Specifically, secretome treatment resulted in a significant reduction in MDA levels, an increase in antioxidant molecules such as glutathione, SOD, and catalase, and a notable decrease in IL-1β levels in rat models of PD [26]. These changes are indicative of a response to oxidative stress and inflammation [85].

Molecular analyses of the secretome have identified several key molecules, including Prdx1, fibronectin, and cadherin-2 [40]. Prdx1, when overexpressed in DA neuronal cell lines, has been shown to mitigate the effects of 6-OHDA by functioning as a ROS scavenger, which enhances the survival and protection of DA neurons [86].

SOD enzymes play a critical role as the first line of defense against ROS, catalyzing the dismutation of superoxide radicals to protect cells, including DA neurons, from oxidative damage [87,88]. Fibronectin exhibits dual roles in the nervous system, contributing both to neuroinflammation and neuroprotection. It can bind to integrins and growth factor receptors, such as the IGF-1 receptor, activating intracellular signaling pathways like the PI3K/AKT pathway. This activation promotes neuroprotective actions akin to those of growth factors, helping to limit apoptosis, prevent microglial activation and neuroinflammation, and regulate ROS accumulation, thereby maintaining oxidative stress levels [89,90].

Histological effect of secretome

In the PD-induced group, shrunken pyknotic and hypoxic changes were observed. Similar morphological alterations were noted in the levodopa-treated group; however, the secretome-treated group exhibited intact neuronal cell architecture, with only occasional pyknosis. This indicates milder neurodegenerative changes compared to both the disease and levodopa-treated groups [26].

In another study involving rats, NSCs were transplanted into the MFB and VTA of PD model rats, which subsequently received secretome therapy derived from MSCs CM or hNPCs CM. The results demonstrated an increased ratio of TH-positive neurons, indicating a rise in dopaminergic neurons in the group that received secretome therapy [40,82]. By week eight, the expansion and migration of neuronal cells in the CM-NSCs group that received secretome therapy showed superior results in histological examinations compared to the group with transplanted NSCs alone [82].

Although a study using secretome from hNPCs reported only a slight increase in TH-positive cells in the SNpc, most studies suggest that secretome administration enhances the number of TH-positive cells and neuronal density in various brain regions, including the SNpc [34,40,81,82,91]. Furthermore, secretome application via direct IC injection resulted in a greater increase in TH-positive cells compared to IV administration, although this increase did not directly correlate with motor function improvements [34].

A comparative study of protein and vesicular fractions of secretomes derived from hBM-MSCs yielded similar results, showing increased TH intensity and survival rates of dopaminergic neurons in the SNpc. However, the increases observed with protein or vesicular fractions alone were not as pronounced as those achieved with the direct application of secretome derived from hBM-MSCs [25].

Additionally, a recent study utilizing the viral vector AAV1/2-A53T-a-syn to induce overexpression of the A53T mutant form of alpha-synuclein in animal models found that treatment with MSC(M)-derived secretome resulted in a higher percentage of TH-positive cells in the SNpc compared to vehicle-treated animals [92–94]. This secretome treatment also led to a reduction in microglial reactivity, suggesting its role in maintaining microglial homeostasis and neuroprotective functions while managing the alpha-synuclein burden in the injured SNpc [92].

Effect of coating material on secretome release

The application of secretome in treating neurodegenerative diseases has shown promising results; however, direct administration often fails to produce long-lasting effects, which is particularly important in chronic conditions like PD [95–97]. To enhance the retention time of the secretome in tissues, a study utilized hydrogels with a semi-interpenetrated polymer system, incorporating COLL, PEG, and LMWHA as coating materials. Two hydrogel combinations were developed: COLL/PEG2000 and COLL/LMWHA. Both formulations demonstrated prolonged availability of the secretome in the tissue, lasting up to 48 hours. Furthermore, the use of these hydrogels for secretome administration resulted in improvements of 26% for the COLL/PEG2000 combination and 24% for the COLL/LMWHA combination following induction with 6-OHDA [98].

Effect of administration route on secretome efficacy

Several studies have explored various administration routes for the secretome, which is typically delivered directly to the brain region. Notably, IV administration, which is less invasive, has been shown to produce effects comparable to those of direct intracranial administration [26]. One study found that administering the secretome via IV resulted in more significant improvements in motor function. However, histological examinations revealed that IC administration led to a greater number of dopaminergic cells [34]. This suggests that while IV administration may be effective for enhancing motor function, IC administration might be more beneficial for promoting dopaminergic cell survival.

Potential of secretome therapy in psychosocial aspect

Motor impairment is one of the most prevalent symptoms associated with PD; however, its effects extend beyond physical limitations to include significant psychosocial challenges. Patients with PD may experience a range of psychosocial disorders, including anxiety, depression, social isolation, and feelings of stigmatization. These perceptions can profoundly affect both the patients and their families [99,100]. Research indicates that such perceptual issues can also hinder social interactions between PD patients and their communities [101].

Recent developments in secretome research have demonstrated promising biomolecular effects and improvements in motor function in animal studies [33,34,40,71,81,91,92,102]. This suggests that secretome therapy has the potential to alleviate motor dysfunction, which is a primary symptom of PD, and may also enhance patients' self-perception. However, it is important to note that there are currently no clinical trials investigating the use of secretome in humans with PD, leaving a gap in objective data regarding its psychosocial effects.

Comparison of secretome and levodopa in Parkinson's treatment

Until now, the use of levodopa is still the mainstay of therapy for PD. The use of levodopa works by increasing the amount of dopamine in the striatum that has degenerated due to PD [103]. Although it has been widely studied, the use of levodopa as a PD therapy still shows some side effects in its use [103,104]. This is possible due to the combination of oxidative and antioxidant effects of levodopa, which in the use of levodopa can occur autooxidation which increases quinones and hydrogen peroxide [104,105]. The existence of this effect causes the use of levodopa to require precise dose adjustments, besides that the improvement effect of levodopa only appears after prolonged use [106,107]. Another factor to consider is how many DA cells are left when levodopa is used because this condition also affects the improvement of the patient's condition [108].

When compared to levodopa, secretome showed a faster effect on motor improvement. This may be because

secretome works on multiple pathways [81]. In addition, the neuroregenerative effect produced by secretome increases the potential for cell differentiation in the brain into new DA cells so that the potential for dopamine production increases. However, the use of secretome in PD patients in humans has not been studied so there is still not much data related to the potential of this therapy in humans.

Perspective of current challenge and future recommendation

Research utilizing the secretome has demonstrated promising preclinical data for its application as a therapy for PD. However, significant variations exist in the types of trials conducted, both *in vitro* and *in vivo*. These variations include the source of MSCs, the methods of secretome production, the routes of secretome administration, and the types of experimental animals used to examine the effects of the secretome.

Differences in the types of experimental animals employed in various studies can lead to differing outcomes in secretome therapy. The choice of animal model often depends on the study's objectives; for instance, cell cultures or organoids can facilitate the analysis of molecular mechanisms, while more complex interactions may require the use of experimental animals such as *C. elegans* or mice. Currently, research has focused more on the molecular effects of the secretome, indicating a need for further studies involving both experimental animals and human trials to better understand the secretome's effects.

In this review, it was noted that MSCs derived from neural-induced stem cells yielded better results compared to those derived from adipose tissue. However, many studies also utilize other stem cell sources, such as bone marrow. Future research should compare the effectiveness and safety of various stem cell types to identify the most suitable progenitor source for secretome production. Additionally, exploring dynamic models for secretome production and employing coating materials to extend the half-life of the secretome is an intriguing area for further investigation, as there is currently limited research on this topic.

Most studies included in this review applied the secretome via intra-cerebral administration in animal research. While this method may complicate its application in human studies, some research has explored intravenous administration. Therefore, expanding studies that utilize intravenous routes may be beneficial. Furthermore, investigating the combination of secretome therapy with existing PD treatments could reveal potential additive effects that enhance current management guidelines.

To fully assess the benefits of the secretome in PD management, further human studies are essential. Phase one clinical trials should be conducted to evaluate the safety, therapeutic dosage, and efficacy of secretome therapy in PD. Human assessments will also allow for a broader evaluation of factors that cannot be addressed in *in vivo* trials, such as psychosocial effects.

Limitation

In searching for journals related to the use of secretome in Parkinson's interventions, a broad keyword search was conducted. However, there are still limited search results on this topic because research on the use of secretome in Parkinson's cases is still in its early stages. The existing results are primarily preclinical studies conducted *in vivo* and *in vitro*, with no studies conducted on humans. Scoping reviews aim to provide a broad overview of a topic, but for this specific topic, research is still sparse. However, this scoping review can already highlight developments in research related to the use of secretome in Parkinson's cases, including biomolecular mechanisms, development of production methods, implementation assessments, histological effects, and more complex effects observed in animal trials, particularly in assessing motor effects. This broad discussion on the use of secretome provides an overview that is not limited to one aspect, aligning with the scoping review's function of presenting a comprehensive view of the topic's development.

Currently, research on the secretome remains primarily in the preclinical phase. Additionally, there are numerous variations in the sources of cell progenitors used to produce secretome, as well as in the research subjects involved. These variations contribute to inconsistencies in research findings, as there is no standardized protocol for secretome production in studies related to PD. Furthermore, there have been no studies investigating the use of secretome in humans with PD, which limits the assessment of its potential in clinical settings.

CONCLUSION

The use of the secretome as a novel therapeutic approach in PD research has demonstrated promising results. This is supported by molecular effects associated with neuroprotection, neurodifferentiation, and anti-inflammatory responses, all of which play crucial roles in the progression of neurodegenerative diseases. Additionally, the application of the secretome has led to improvements in motor and behavioral functions that are often impaired in Parkinsonian models. However, current research on secretome therapy for PD is primarily limited to laboratory studies involving experimental animals. To advance the clinical application of secretome therapy for patients with PD, further research, particularly phase one clinical trials in humans, is essential.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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The authors declare that there is no conflict of interest.

ETHICS APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

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USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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