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Metallic Nanomaterials in Parkinson's Disease: A Transformative Approach for Early Detection and Targeted Therapy

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Abstract

Parkinson's disease (PD) is a progressive neurodegeneration where there is substantial dopaminergic neurons loss in the substantia nigra, causing both motor and non-motor symptoms that significantly impact the quality of life. The prevalence of PD is expected to increase with the aging population as it affects millions globally. Current detection techniques, including clinical assays and neuroimaging, lack the sensitivity and specificity to sense PD at its earliest stages. Despite extensive research, there is no cure for PD, and the available treatments primarily focus on symptomatic relief rather than halting disease progression. Conventional treatments, such as levodopa and dopamine agonists provide limited and often temporary relief, while long-term use is associated with significant side effects and diminished efficacy. Nanotechnology, particularly the use of metallic-based nanomaterials (MNMs), offers a promising approach to overcome these limitations. MNMs, due to their unique physicochemical properties and can be engineered to target specific cellular and molecular mechanisms involved in PD. These MNMs can improve drug delivery, enhance imaging and biosensing techniques, and provide neuroprotective effects. For example, gold and silver nanoparticles have shown potential in crossing the blood-brain barrier, providing real-time imaging for early diagnosis and delivering therapeutic agents directly to the affected neurons. This review aims to reveal the current advancements in the use of MNMs for the detection and treatment of PD. It will provide a comprehensive overview of the limitations of conventional detection techniques and therapies, followed by a detailed discussion on how nanotechnology can address these challenges. The review will also highlight recent pre-clinical research and examine the potential toxicity of MNMs. By emphasizing the potential of MNMs, this review article aims to underscore the transformative impact of nanotechnology in revolutionizing the detection and treatment of PD.

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1. Introduction

Parkinson's disease (PD) is a public debilitating progressive neurodegenerative disease affecting the elderly. It is predominant in the second place after Alzheimer disease. PD prevalence increased in the last 40 years compared to the previous period reaching about 9% among the elderly population over 60 years with higher incidence in males. This gender-related occurrence is thought to be due to the doubtful neuroprotection of estrogen. [1], [2] According to the WHO, it is expected that the PD affected population will rise up to about 2 million at 2030. [3], [4] Although the etiology of PD is precocious in terms of clarity, PD is attributed to either non-genetic factors as dietary imbalance and pesticides or genetic mutations related to α-syn and dopamine which is more prevalent in patients less than 40 years. [3],[5] To achieve definitive diagnosis and efficient therapy, the pathophysiology of PD should be elucidated. PD etiology is not fully understood. Hitherto, deciphering research is recruited to provide coherent and substantial mechanistic explanation.

The dopaminergic neurons of the substantia nigra (SN) provides the dopamine for the striatum. In PD, the substantia nigra pars compacta (SNpc) neurons, that are responsible for the motor functions, are disrupted, and privation of the extracellular dopamine in the synapse culminates the striatal malfunction and induces motor disability. [6], [7], [8], [9] Other coherently pertinent factors that abrogate the PD ailment are the altered mitochondrial functions, triggered cerebral inflammatory response, and exacerbated ROS generation and activation of microglia. [10], [11], [12]

Remarkably, the aggregation of the α-synuclein (α-syn) and formation of Lewy bodies within the dopaminergic neurons of the substantia nigra is one of the main hallmarks. α-syn protein is formed from 140 amino acids divided into 3-regions; N-terminal, amyloid-binding central domain and the C-terminal. The first region is responsible for the protein's aggregation where the phosphorylation of serine-129 within the last region abrogates this event. [13], [14,15] The aggregation of the α-syn contributes in the dissipated dopaminergic neurons within the SNpc leading to dopamine deficiency. [16], [17]

The PD development and progression is mostly explained by the Braak hypothesis that divides the disease into six stages where the symptoms starts with olfactory disorders and ends by the cognitive impairment. [18], [19] PD symptoms can be classified as motor and non-motor symptoms as

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well (**Fig. 1**). Neuromotor disability is mainly observed as tremors at rest and bradykinesia. The latter class is heterogenous and includes cognitive disorders in addition to fast movement of the eye and some non-PD specific symptoms. All these symptoms culminate the declined life quality and can occasionally embars the patients. [20], [21], [22], [23] The focus of this review will be the inciting development of metallic nanomaterials (MNMs)-based detection techniques, therapeutics and theranostics. Furthermore, toxicity, biocompatibility, challenges, and future outlook would be delineated.

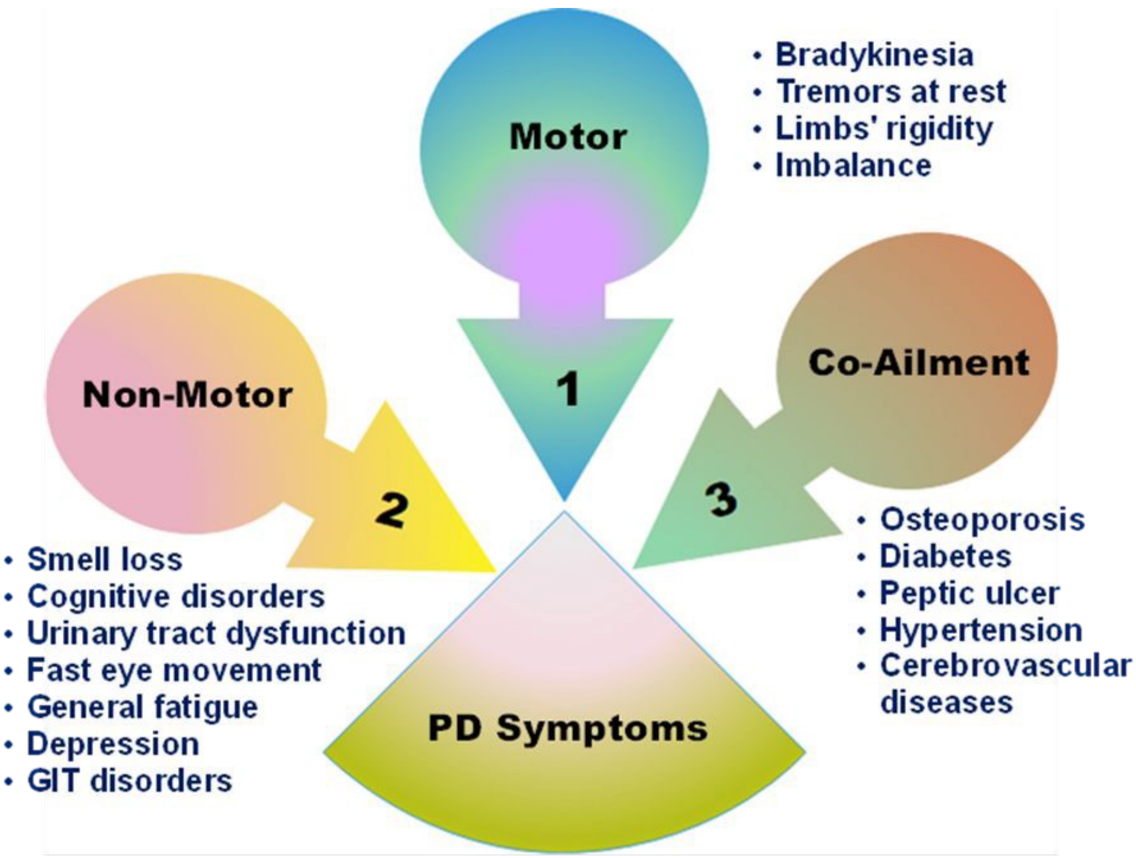

Fig. 1. A summary of the PD symptoms [20], [24],[25]

2. *Detection of PD*

PD clinical diagnosis remains challenging and misleading in most cases due to the overlap of its symptoms with other neurodegenerative disorders. Intriguingly, accumulation of misfolded α-syn protein clumps and development of lewy bodies in various brain parts is evident to be the primary pathogenic hallmark of PD. These α-syn aggregates, as well as DA, levodopa (LD), and miRNAs, form essential biomarkers for the early identification and control of this disease. [26–29] Current

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diagnostic platforms involve enzyme linked immunosorbent assay (ELISA), fluorescent and electrochemical immunoassays, high-performance liquid chromatography (HPLC), real-time polymerase chain reaction (rt-PCR) and neurobiosensors. [26,30,31] ELISA is the most commonly used method for the detection of markers like PS65-Ub indicating any mitochondrial dysfunction and α-syn especially in CSF because its levels are higher than in biofluids. [32] Other methods, like electrochemiluminescence and immunomagnetic reduction, are becoming more common and undergo more developments to detect extremely low levels of biomarkers. [33]These conventional techniques are used to selectively detect and quantify the levels of DA and α-syn in body fluids like blood and urine [34]. However, they suffer from several pitfalls; they can be complex, expensive, time-consuming, insufficient accuracy and false results, and require result interpretation. [34,35]

Molecular imaging techniques are also implemented in PD diagnosis; they include magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), positron emission tomography (PET), transcranial ultrasound imaging and their advancements. They provide quantitative information about structural changes in the brain according to their modalities and computer algorithms, and utilize tracers and contrast agents to bind to specific targets and markers. [36–38] Nevertheless, they are still expensive and labor-intensive techniques and this limits their accessibility for PD patients.

2.1. *Artificial intelligence (AI)-based PD detection*

With the outgrowing need for development and advancements of PD differential diagnosis, scientists have implemented and integrated artificial intelligence (AI) and machine learning (ML) in this process. They have employed data analytics to accurately diagnose PD in the early stages and it is showing promising results. AI holds a great potential for the automation of diagnosis and its accessibility in remote areas with high demands [39,40]. They mainly depend on using different models and algorithms to process inputs according to well-established libraries. These inputs can be medical history, genetic information, symptoms or PET images that need expertise to be analyzed. Such inputs are provided to AI systems possibly through wearable devices (WDs) so that they can detect patterns and anomalies indicating PD incidences with remarkable precision. Even breath patterns, as shown in **Fig.2**, were proved to have a link with PD, where a study was conducted on nocturnal breath signals to predict the disease. [41] The developed model achieved

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specificity and sensitivity of 82.83% and 86.23%, respectively using wireless signals. While ML uses algorithms to enable computers to process data without being programmed, deep learning (DL) exploits more sophisticated multi-layered neural networks for more complex data analysis and accurate predictions. [39] This allowed expansion of sample size, reaching remote places, early decision making, and optimizing more algorithms to outperform human expertise. Moreover, WDs emerged as a promising tool that allows the non-invasive detection and continuous monitoring of PD. They have advanced sensors that capture motion patterns and physiological signals real-time and collect data to analyze motor functions indicative of PD patient. The design of these devices was integrated with AI to aid in data interpretation and highlight any deviation from normal motor functions.[42] AI also facilitates the continuous improvement of WDs and adaptation through learning from any new inputs for further enhancement of the accuracy. [43] Besides, different types of sensors were exploited in WDs such as inertial, acoustic, optical, electrical, and force sensors. Once the patient uses the device, it begins retrieving and collecting specific data to be processed and analyzed using different AI and DL or ML models and algorithms. [44] However, this technology suffers from several drawbacks; ML models implemented in the studies lack full description of findings or techniques. Moreover, number and kind of subjects and their medical history are not accurately reported and assessed; while, DL models are limited due to difficulty in handling of their datasets. [45,46]

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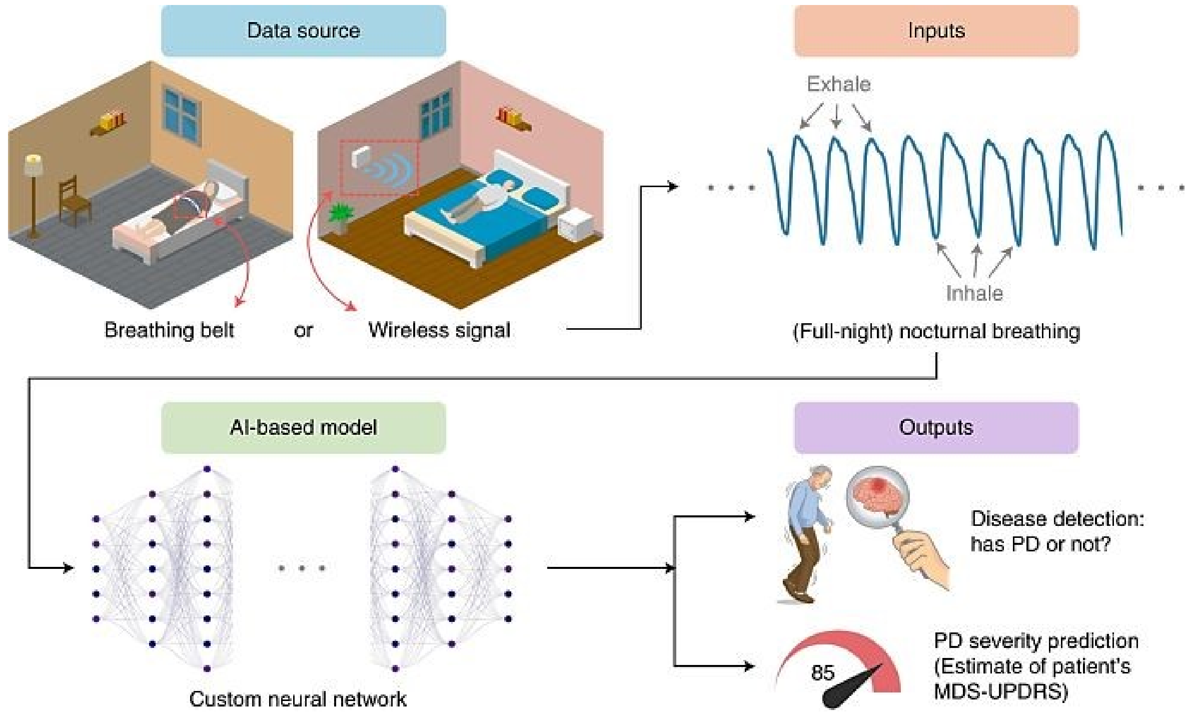

Fig. 2. A schematic illustration showing the process of AI-based diagnosis of PD. Breathing patterns is collected through signals or wearable device and processed using AI models. Based on the analysis, PD is predicted if present and its severity is determined according to Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) questionnaire. Reproduced from reference [41].

2.2. MNMs-based biosensors for the detection of PD

Nanotechnology holds great potential to overcome the aforementioned challenges and confer revolutionary advances in developing diagnostic assays to enable the early detection of this incurable neurological disorder. Even though the mechanism of nanomaterials in biosensing remains unclear, they are currently experimented with offering high sensitivity, specificity and low limit of detection (LOD) [47]. Metallic nanoparticles (MNPs), like gold and silver nanoparticles, exhibit unique tunable electronic and optical properties enabling them to be used for imaging of PD. They can interact with incident light and form characteristic absorption signals that shift depending on their sizes and shapes. [48] Moreover, they can be functionalized with specific chemical moieties to be able to cross the blood brain barrier (BBB) and act as contrast agents or bind to any desired biomarker and quantify it with high sensitivity [49–51]. Different metals can be

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used to develop diagnostic assays for the detection of PD depending on their properties and the type of sensors. [52,53] For instance, a study was conducted to develop an immunosensor based on electrochemical impedance spectroscopy. They used an electrode system modified with Palladium nanoparticles (PdNPs) to enhance the signals and the conductivity. This PdNPs-plated electrode was functionalized with α-syn antibodies to quantify the levels of α-syn and epinephrine in clinical serum samples. It showed linear response in phosphate buffer and serum samples with LOD of 0.13 µg/ml and 1.3 µg/ml, respectively. [54] Based on that, research has recently focused mainly on exploiting MNMs to enhance the sensitivity and performance of different types of biosensors. Biosensors can be categorized into immunosensors, DNA- and enzyme-based biosensors, and piezoelectric and thermal biosensors. [35,55] This review will focus mainly on different MNMs like zinc, platinum, gold, silver, cerium, and iron in the fabrication of biosensors for the detection and imaging of PD.

2.2.1. Gold nanoparticles (AuNPs)-based biosensors for the detection of PD

The nanoparticles of the noble metal gold (AuNPs) are extensively used for the detection of PD owing to the ease of fabrication, their inert nature, large surface area, and high affinity to biomolecules. [56] In addition, they are biocompatible and good conductors of electricity, and they have unique optical properties manifested in their surface plasmon resonance (SPR). SPR is related to the oscillation of conducting electrons resulting in a distinguished absorption profile that depends on the shape and size of AuNPs. On account of this phenomenon, they are considered as signal transducers as shown in **Fig. 3A.**[57,58] Moreover, they have been used in different structures to construct simple and sensitive biosensing platforms to enable the rapid and early detection of biomarker of PD as shown in **Fig 3B**. For instance, biotinylated antibody-conjugated AuNPs combined with graphene were used to design an electrochemical immunosensor to linearly detect the concentration of α-syn antigen in plasma. This nanocomposite enabled immobilization of the antibody, enhanced the conductivity, sensitivity, and specificity of the immunosensor, and produced higher current peak of 5.5 µA. Moreover, its electrochemical performance was investigated using square wave voltammetry (SWV) and showed linear detection of the antigen from 4 – 128 ng/ml with LOD of 4 ng/ml. However, the immunosensor stability and reproducibility were still under investigation before it can be used as a point-of-care device. [31]

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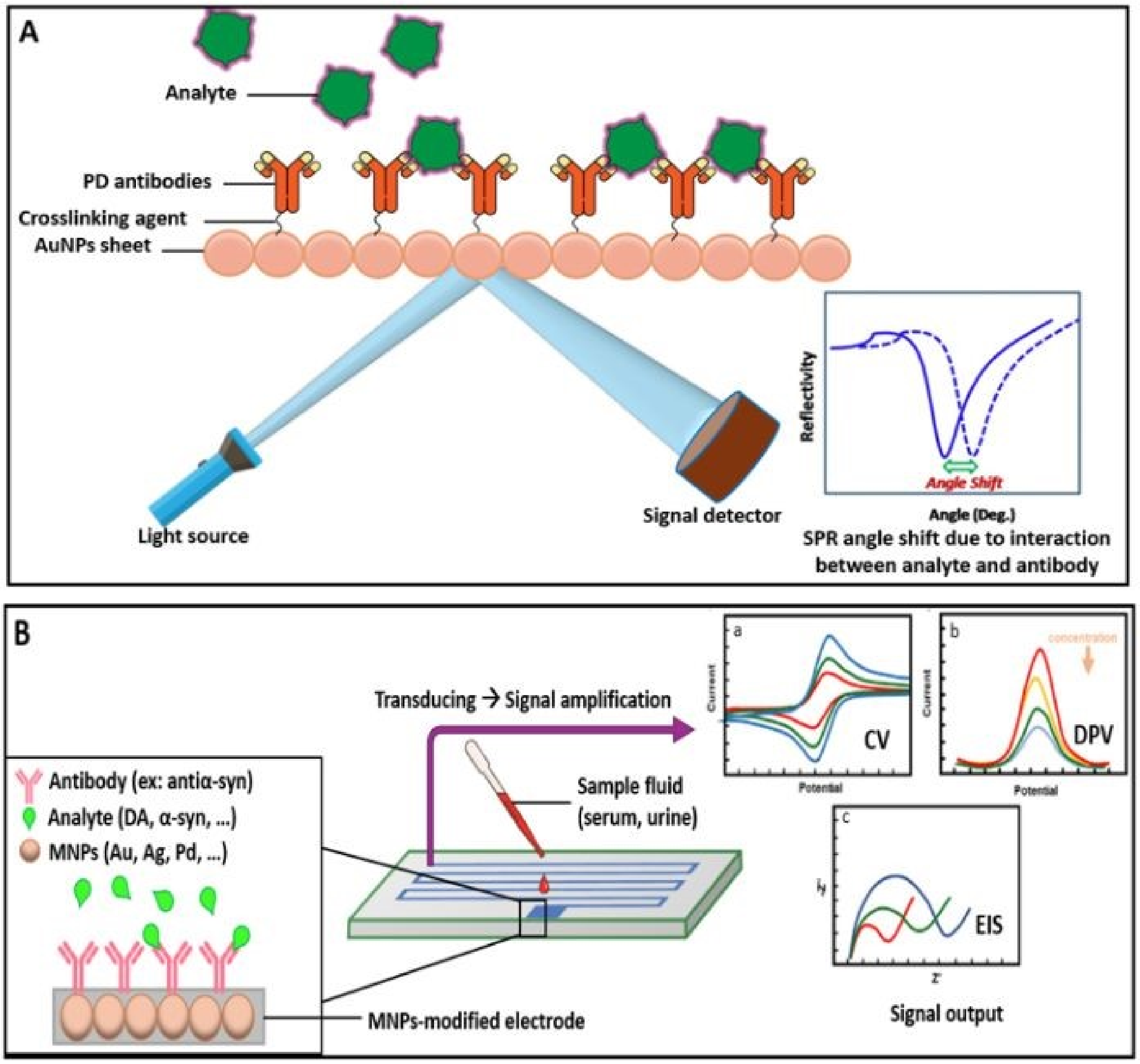

Fig. 3. (**A**) Schematic illustration of SPR phenomenon of AuNPs and its implementation in a diagnostic platform, where the interaction between the antibody and the analyte (target) causes SPR signal to shift indicating the presence of the target. (**B**) Schematic illustration of an electrochemical biosensor exploited in PD diagnosis. The antibodies are linked to an electrode, and the presence of the analyte alters the electrical signal output whether in the form of (**a**) cyclic voltammetry (CV) signal, (**b**) differential pulse voltammetry (DPV) signal, and (**c**) electrochemical impedance spectroscopy (EIS) signal.

Another research work was performed using activated charcoal modified with AuNPs to detect the levels of LD in synthetic serum, urine, and river water. This nanocomposite was deposited on a

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glassy carbon to fabricate an electrode that measures the electrochemical response of LD using square-wave adsorptive anodic stripping voltammetry. Various factors were also studied according to Doehlert experimental matrix to assess their impact on the electrode performance. The results showed linear detection of LD and LOD of 50 nmol/L – 10 µmol/L and 8.2 nmol/L, respectively.[34]

Several studies were also conducted using the same integrated nanocomposite with different carbon allotropes to construct an electrochemical immunosensor. The reason is that it proved to have high surface area and conductivity, unique electronic properties, and biocompatibility. For example, recent work was done using multi-walled carbon nanotubes with AuNPs-doped modified with indium tin oxide electrode. This electrode was developed to detect levels of DJ-1 protein as a biomarker of PD in cerebrospinal fluids and saliva. Analysis of the biosensor efficiency was conducted using electrochemical impedance spectroscopy (EIS), single frequency impedance, and cyclic voltammetry (CV) and it showed detection range and LOD of 4.7 – 4700 fg/ml and 0.5 fg/ml, respectively. [59,60]

Carbon nanotubes were also used in another work as single-walled (SWCNTs) to fabricate interdigitated electrode functionalized chemically with anti-α-syn-conjugated Au nanourchin.[56] This electrode was designed to detect the levels of α-syn and the results were confirmed using ELISA technique. Due to integrating Au nanomaterial to the electrode, higher sensitivity and selectivity were achieved because it can detect low currents. Therefore, LOD was enhanced from 1 pM using the bare SWCNTs electrode to be 1 fM after applying conjugated gold nanourchin.[56]

A different study was conducted using labelled gold nanobipyramids (GNBPs) to construct lab-on-a-chip diagnostic system based on surface-enhanced Raman scattering (SERS). This nanostructure is anisotropic which offered sharp tips and edges and consequently, enriched the plasmonic hot points. In addition, it was functionalized with hairpin DNA and Raman reporter moieties which caused GNBPs to aggregate if the analyte was present. This platform enabled the detection of altered expression of miR-221 and miR-214 as biomarkers of PD through amplified SERS signal due to aggregation. [61]

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SERS technique was also implemented in another study conducted on AuNPs. However, this study aimed at imaging DA in retinal tissues and live cells. AuNPs were labelled with modified thiol molecules due to their high affinity to Au surface where DA-positive samples result in the aggregation of functionalized AuNPs. The positive response was detected by the Raman scattering signals due to formed plasmonic hot spots, and it is speculated that this technique can be further applied in the detection of DA in live cells in PD patients.[62] Furthermore, the biodistribution of administered gold nanoclusters (AuNCls) was studied as a function of the route of administration in mice as animal models. Intravenous, intraperitoneal, intranasal, intragastric routes were assessed, and it was found that AuNCs were mostly located in the brain in the case of intraperitoneal administration. This implies that they had the ability to cross the BBB, therefore, can be further investigated to use such nanoparticles in the imaging of PD upon irradiation along with treatment.[63] Besides, Adam et el. focused on developing AuNPs-based interdigitated tetraelectrode to detect α-syn in the fibril formation process. This electrochemical biosensor was investigated using cyclic and differential pulse voltammeter, and the results showed linear range of 1 aM – 1 pM and LOD of 100 aM. [64] All these biosensing models will enable the early detection and monitoring of PD once they are well-developed and pass the stages of the clinical trials.

2.2.2. Silver nanoparticles (AgNPs)-based biosensors for the detection of PD

Silver nanoparticles (AgNPs) were investigated in literature for the detection of PD by biosensing of different PD biomarkers.[65] Like Au, Ag has unique SPR properties, good chemical stability and biocompatibility, and enables Raman spectroscopy. For example, Ma et al. exploited silver nanoclusters (AgNCls) functionalized with 5-mercapto-2-nitrobenzoic acid (MNBA) to fabricate photoelectrochemical biosensor to detect the levels of DA and glutathione (GSH), simultaneously in PD-bearing animal models with different stages. The cell structure was designed using Ag electrodes as multi-channels for the detection of multiple analytes through changes of photocurrent. AgNCls were further integrated with hybrid nanomaterials like graphene oxide (GO), carbon dots (CDs), and AgNPs to enhance the photoelectric activity, sensing performance, and the selectivity. The results showed that the biosensor hybrid with AgNPs and GO achieved LOD and linear range of DA of 53 nM and 0.16 – 6 µM, respectively. Whereas, the biosensor hybrid with CDs reported LOD and linear range of GSH of 34.3 nM and 0.1 – 1 µM, respectively.[26] Another work employed AgNPs to fabricate label-free SERS platform as a sensitive and robust

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diagnostic assay to detect 5-S-Cysteinyl-DA which is an important metabolite in PD. The results showed that this technique allowed the detection of the metabolite in synthetic cerebrospinal fluid with low concentrations of about 10 nM while 100 nM in simulated urine. [66]

The same technique was implemented in another work to detect the levels of DA in-situ using AgNPs where the label-free SERS measurements were conducted with laser of wavelength 488 nm. The results displayed reproducibility of SERS spectrum when using citrate-reduced AgNPs upon binding to DA through surface adsorption. [67] Besides, Rouhani et al. worked on developing a biosensing electrode made of AgNPs with GO as a nanocomposite to detect LD in serum and urine samples. The performance of the modified electrode was measured through CV, and it showed enhanced oxidation-reduction peaks. Different parameters, such as concentration of GO, pH, and accumulation time were optimized, and the results showed that this accurate assay achieved LOD of 0.76 nM and linear range of 0.003 – 10 μM of LD. [68]

2.2.3. Iron oxides nanoparticles (IONs)-based biosensors for the detection of PD

Avowedly, iron oxides nanoparticles (IONs) are extensively used in the bioimaging and biosensing of neurodegenerative diseases due to their inherent biocompatibility, biodegradability, and small tunable sizes. [69] They also exhibit unique SPR properties and high refractive index, therefore, they can cross BBB and serve as excellent MRI contrast agents in clinical bioimaging. Moreover, they can be functionalized with specific chemical moieties for enhancing the active targeting and bypassing BBB. Superparamagnetic IONs (SPIONs) align and become magnetic in the presence of external magnetic field, and this property can be employed for sustained drug release, control the targeting and avoid the clearance. [57] Furthermore, SPIONs have also been used to tag, track, and monitor stem cells and their spatial distribution via MRI. [70] An et al. managed to synthesize ultra-small IONs functionalized with polyacrylic acid (PAA) and polyethylene glycol (PEG) to prevent protein corona formation and reduce the immunogenic response *in-vivo*. These particles acted as effective MRI agents with relaxation rate of 84.65/s.mM and they enabled labeling and tracing of primary human adipose-derived stem cells for up to 3 weeks. [71] This can be further implemented as a diagnostic technique to trace potentially therapeutic stem cells in PD patients.
Another study employed PEGylated SPIONs conjugated to W20 antibody as MRI probe to detect amyloid oligomers in PD transgenic mice. The results proved the BBB penetration of these small

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SPIONs and showed high magnetic resonance relaxation and significant contrast in T2 weighted image. Therefore, this system was able to detect amyloids at the early stages because of its high sensitivity and biocompatibility. [72] Additionally, magnetic IONs were exploited in the biosensing of different biomarkers of PD due to the ease of their functionalization and their high sensitivity. For instance, Yang et al. developed a sensitive immunosensor depending on immunomagnetic reduction (IMR) of magnetic IONs labelled with anti-α-syn. The IMR signals in plasma samples were detected with magnetosusceptometer and the results showed that they achieved LOD and range of α-syn concentration of 0.3 fg/ml and 0.1 – 100 pg/ml, respectively. [73,74] Another work was done using anti-α-syn-functionalized IONs hybrid with GO to construct Mg-based micromotors for the detection of α-syn in whole blood samples. This sensitive electrochemical biosensor enabled the effective capturing of the biomarker in 100 s and its concentration was inversely proportional to the signal amplification capability of the developed biosensor. [75] Besides, Zhang et al. investigated IONs-based interdigitated electrode for the identification of α-syn through using both aptamer and antibody to sandwich the analyte. They enhanced the performance of this biosensor by modifying it with AuNPs where the current changed as a response to binding to the target in a linear manner. The results recorded LOD of 10 aM and a linear range of $10 – 10^7$ aM with $R^2 = 0.9729$, thus, enabled the sensitive and accurate detection of α-syn (**Fig. 4).** [76] **Table 1** summarizes the main studies of MNMs-based biosensors of PD.

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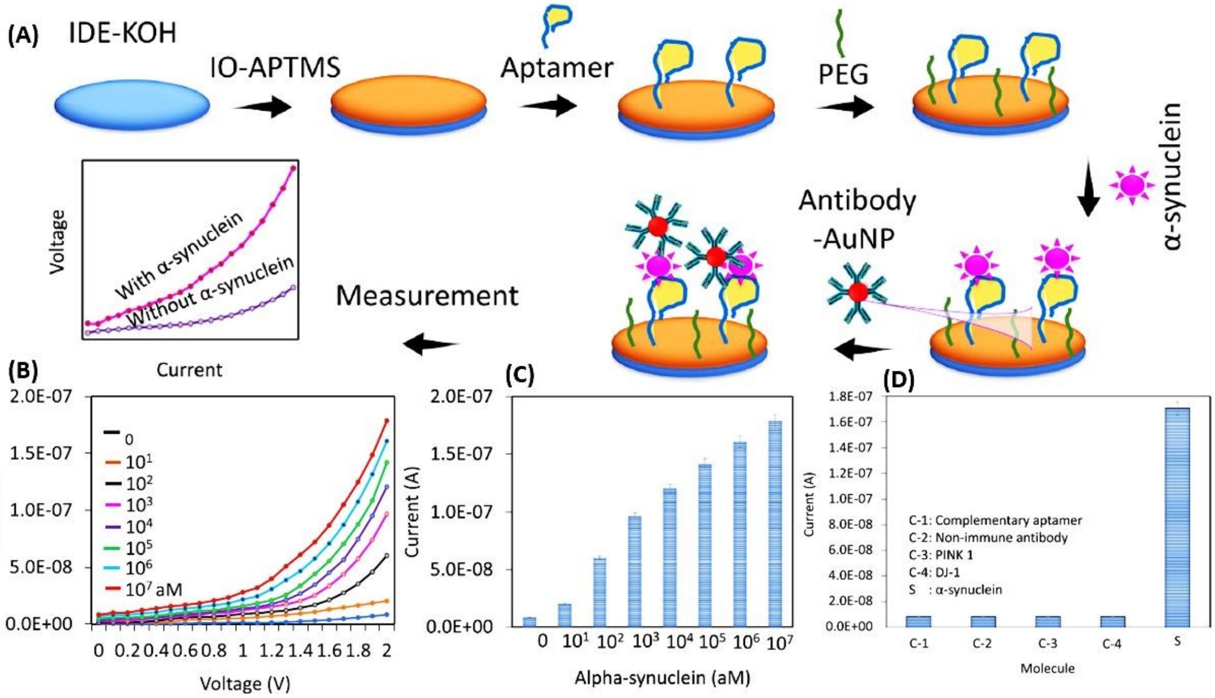

Fig. 4. (**A**) Scheme of the biosensor building. Iron oxide (IO)-modified aptamer and polyethylene glycol (PEG) were immobilized on the surface of interdigitated di-electrode (IDE) where the α-syn is sandwiched by the anti-α-syn aptamer and antibody-AuNPs, (**B**) and (**C**) quantitative detection of α-syn several concentrations and (**D**) selective detection of α-syn in the presence of other analytes. Reproduced from reference [76]

Table 1. Summary of the main studies reported the development of MNMs-based PD biosensors.

Target	Targeting Ligand	Sample Type	Detection Method	Nanomaterial	Linear Range	LOD	Ref.
α-syn	rabbit Ab138501 mAb	Serum	Label-free SPR	Iron oxide (Fe_3O_4) NPs	0.01 – 100 pg/ml	5.6 fg/ml	30
α-syn	Specific antibodies	Synthetic cerebrospinal fluid	Electrochemical impedance spectroscopy	Palladium (Pd) NPs	1.5 – 15 µg/ml	0.13 µg/ml	54
Epinephrine	----				0.75 – 100 µmol/L	0.051 µmol/L	
DA	----	Live human nerve cells	Enzyme-less electrochemical biosensor (CV)	NiAl layered double hydroxides nanosheets integrated with GO	0.1 – 97 µM	2 nM	77
α-syn	antiα-syn	Diluted human sera	Label-free electrochemical immunoassay	Cysteamine-functionalized fluorine-doped tin oxide NPs	10 – 1000 ng/ml	1.13 ng/ml	78
	antiα-syn	Human plasma	Electrochemical immunoassay	Gold Nanostars-decorated zinc oxide (ZnO) nanowires	0.5 – 10 pg/ml	0.08 pg/ml	79
	Monoclonal antibody	Plasma and serum	Immunomagnetic reduction assay	Magnetic Fe_3O_4 NPs	ND	In plasma: 3.60 ± 2.53 pg/ml In serum: 0.03 ± 0.04 pg/ml	80
	Thiolated aptamer	Diluted serum	Electrochemiluminescence (ECL)	AuNPs@Metal organic frameworks (MOFs) composite	2.43 fM – 0.486 pM	0.42 fM	81
	Carboxylated aptamer				1.39 fM – 0.243 pM	0.38 fM	

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These MNPs-based electroanalytical techniques have advantages over conventional ones as they require small volume of sample and exhibit high sensitivity and specificity. They also allow multiplexing where one electrochemical biosensor can be functionalized with various ligands for the detection of multiple analytes simultaneously, and this, as a return, enhances the accuracy of the result. As for the imaging techniques, contrast agents, like IONs, enabled higher resolution in MRI and easy penetrability due to their ultra-small sizes, and they can detect any minor changes in the brain structure. However, using MNPs may encounter some limitations where they can be expensive to manufacture, complex according to the design, and difficult in standardization because of the low reproducibility and high reactivity of the nanoparticles. These hurdles require more advanced research and optimization in implementing nanotechnology in diagnostic techniques to overcome such limitations and enhance the nanoparticles applicability.

3. *Treatment of PD*

BBB is a semi-permeable membrane that surrounds the central nervous system including the brain. It confers selective permeability that constrains the passage of pathogens and toxins but passively transport the essential nutrients for survival and homeostasis. [82] On the other hand, this semi-permeability constrains the treatment as only 1% of the therapeutic doses reaches the brain. However, increasing the doses is stumbled by the severity of the adverse effects. [16], [83] PD is irremediable and the available therapy is mainly palliative for both the motor and non-motor symptoms. Therefore, the patients' plight is ameliorated through the easiness of the symptoms by increasing the intraneuronal dopamine (DA) or enhances DA receptors. [20] Due to the noted DA deficiency in the PD patient's brains, the recruited efforts lead to the development of DA precursor; levodopa (L-3,4-dihydroxyphenylalanine, known as L-dopa). L-dopa is characterized by its ability to penetrate the BBB and converted into DA when absorbed by the nerve cells. Hitherto, the DA precursor; L-dopa, is the indispensable choice for the treatment and it exerts its effect through replenishing the deficiency. L-dopa can be undesirably converted to DA in the peripheral nerves, therefore, carbidopa (peripheral dopa-carboxylase inhibitor) is co-administered with L-dopa.[84] However, DA does not exert efficient remedial effect on the non-motor symptoms as hallucination and can culminate dopaminergic "type A" adverse effects.[85] Also, there are some drugs classes that were proven to have anti-PD effect as monoamine oxidase-B (MAO-B) inhibitors and catechol-O-methyltransferase (COMT) inhibitors. However, they may also induce the

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dopaminergic "type A" adverse effects. [85] Different treatment mechanisms are illustrated in **Fig. 5.**

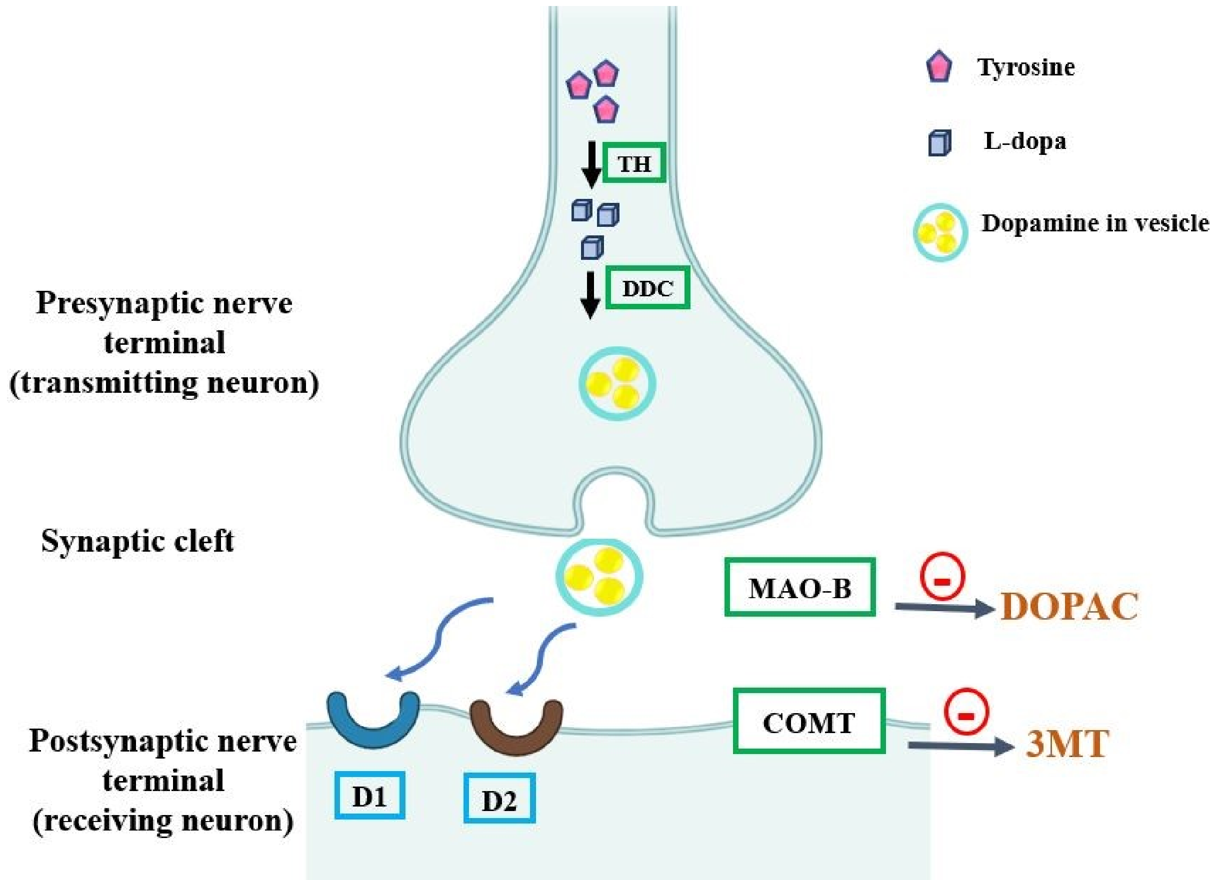

Fig. 5. Classes of anti-PD drugs affecting the DA (dopamine) synapse. In the presynaptic nerve terminal, tyrosine is converted to L-dopa by tyrosine hydroxylase (TH) and then to DA by L-dopa-decarboxylase (DDC). Monoamine oxidase-B (MAO-B) inhibitors prevents DA break down and catechol-O-methyltransferase (COMT) inhibitors prevent L-dopa peripheral degradation. D1 and D2 are DA agonists as the non-ergot agonists. DOPAC, dihydroxyphenylacetic acid; 3MT, 3 methoxy-tyramine. Recreated from reference [86].

The resistance-dependent debilitating ability of the neurons to maintain the DA in addition to the limited plasma half-life of L-Dopa aggravates the PD motor stability. For instance, the DA level fluctuates causing on/off cycles of akinesia and dyskinesia. So, non-ergot DA agonists as ropinirole and pramipexole are currently used as long-acting treatments available for PD. [86, 21] In order to sequester the limitations of PD, the application of nanotechnology and development of

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nano-based therapeutics emerged as efficient and probable definitive treatment. Nanomaterials can penetrate the BBB, interact with the cells, encapsulate and deliver drugs to obtain desirable drug release rate while dissipating off-targeting of the drugs. [87],[88] Intriguingly, many studies have shown the ability of the MNMs to overcome this permeability obstacle and effortlessly penetrate the BBB [89]. Consequently, the MNMs effect is potentiated to have a crucial role in the developing of central nervous system (CNS) novel treatments (**Fig. 6**). Other classes of nanostructures are described in literature elsewhere as liposomes [90], nanoemulsions [91] and polymeric nanoparticles. [92]

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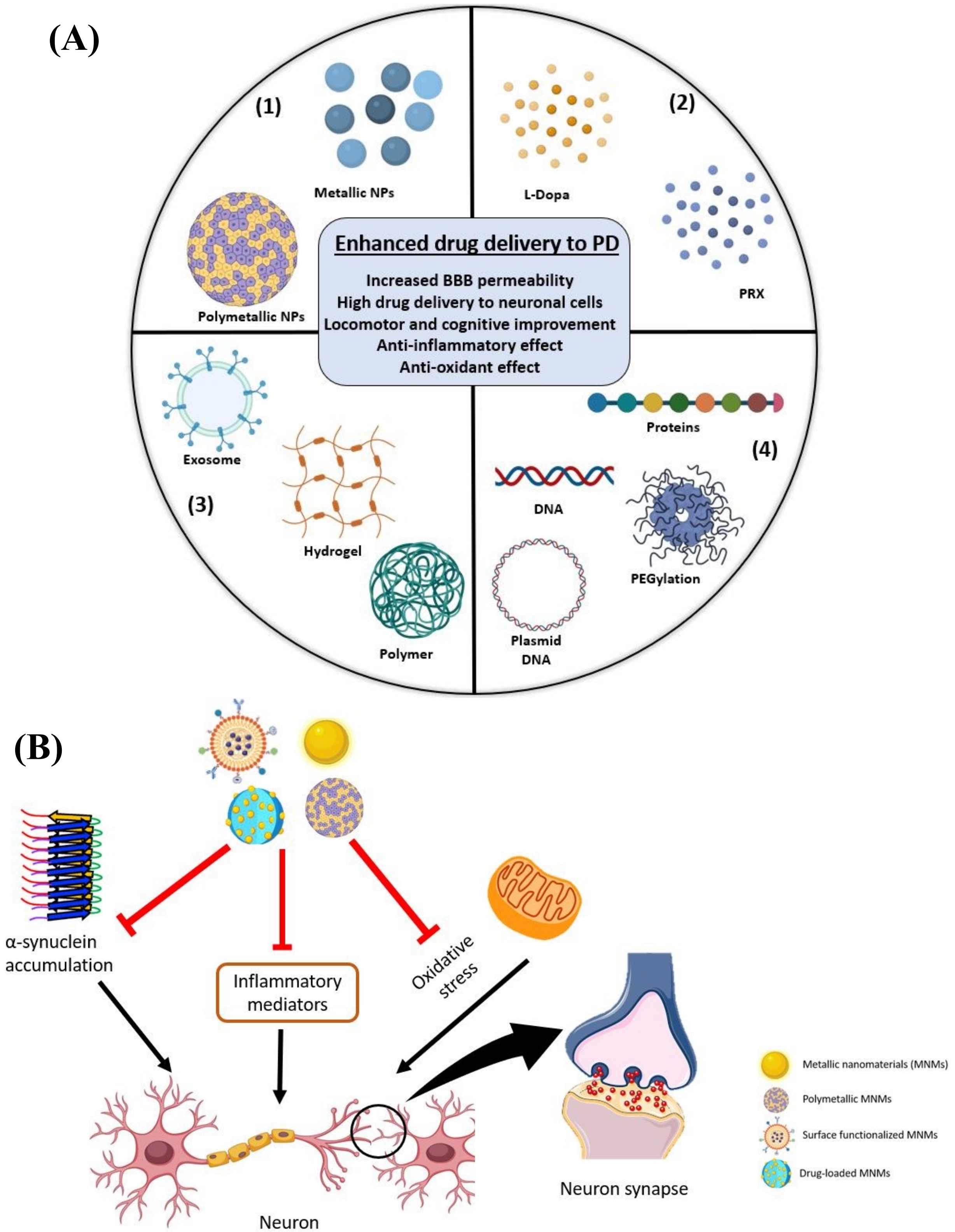

Fig. 6. (**A**) Schematic representation of several protocols for the implementation of MNMs to develop PD-based drug delivery platform. MNMs can be prepared from a single metal or multiple

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metals (**1**), loaded with drugs (**2**), impeded into nanoformulations (**3**) and different classes of surface-attached targeting ligands (**4**), (**B**) Scheme of how the MNMs exert their anti-PD effect through decreasing α-syn level and blocking inflammation and oxidative stress to normalize the neurons' function.

3.1. MNMs-based treatment of PD

3.1.1. Gold nanoparticles (AuNPs)-based systems for the treatment of PD

Gold-based nanostructures have been extensively exploited in biomedical applications due to their biocompatibility, inertness and the presence of versatile well-established preparation approaches. Several factors govern the use of AuNPs such as the size, shape, charge, incorporation within nanoformulations and the use of specific surface-modified ligands, DNA or proteins. Concerning the CNS specifically, AuNPs intrigued specific interest due to their capability to cross the BBB and their antioxidant and anti-inflammatory effect without significant toxicity. [89] To consolidate the importance of size, Gao and coworkers reported the inversely proportion relation between the size of the AuNPs and the intensity of Aβ fibrillation. For instance, relatively bigger AuNPs (36 and 18 nm) enhanced the fibrillation while small AuNCs (6 nm) constrained this process. Intriguingly, even smaller AuNCs (1.9 nm) showed utter fibrillation. [93] Ultrasmall nanoclusters (AuNC, <3 nm) were used to develop remedial nanoformulations for PD [94], [95], [96] due to their remarkable penetration of the BBB. [97] For example, Ma et al, formulated AuNC coated with peptides that are either positive or negative. Both types bind to 20S proteosome. Nonetheless, the AuNC(-) preferentially conferred cellular neuroprotective effect simultaneously with decreasing of α-syn. [95] This study highlighted the impact of different surface charges on PD manifestations and the shape also represented a controversial aspect in terms of its effect. Wang et al, compared Au nanospheres (AuNSs) and Au nanocubes (AuNCs) of the same size (20 nm) and found that AuNSs induce more fibrillation of amyloid-β peptide (Aβ(1-40)) more than {100}-faceted AuNCs owing to the greater chemical activity of the surface atoms. [98] Additionally, the stabilizers of the AuNPs were found to have a potentiation effect. Citrate-stabilized AuNPs were reported to decrease the membrane potential by binding to glia neurotransmitters receptors and thus, neutralize the astrocytes activation. [99] Their release causes diverse neurological disorders as PD through the activation of astrocytes by surface-attached receptors. [100]

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Naturally derived AuNPs were found to be effective treatment for PD [101],[102] and can ameliorate the induced neurotoxicity through exerting protective effect from destructive oxidation, inflammation and cell death.[103] For instance, AuNPs from *Hibiscus sobdariffa* and from have been reported to have remedial effect on PD by abolishing the aggregation of α-lactalbumin.[101] AuNPs (30-50 nm) derived from *Cinnamomum verum* neutralized the oxidative activity and neuromotor dysfunction in the MPTP-induced PD model in addition to mitigated tumor necrosis factor-α (TNF-α), Interleukin-1β (IL-β) and Interleukin-6 (IL-6) levels and normalized TLR/NF-κB signal.[104] Hu, et al., adopted gene drug delivery for the treatment of PD using a nanocomposite based on chitosan and AuNPs loaded with plasmid DNA and nerve growth factor (CTS@GNP-pDNA-NGF) (**Fig. 7)**. The NGF facilitated the cellular endocytosis into the PC12 cells *in-vitro* model. Also, the MPP^+-based apoptosis was inhibited by the nanocomposite as proven by confocal microscope due to the suppressed overexpression of α-syn. These results resembled those obtained from the western blot analysis that proved that CTS@GNP-pDNA-NGF deteriorated the expression level of α-syn. Additionally, in the PD *in-vivo* model induced in C57bl/6 mice by MPTP, CTS@GNP-pDNA-NGF nanocomposite improved the body weight, healed the substantia-nigra density, crossed the BBB and cleared from the body through the spleen after exerting its therapeutic effect.[105]

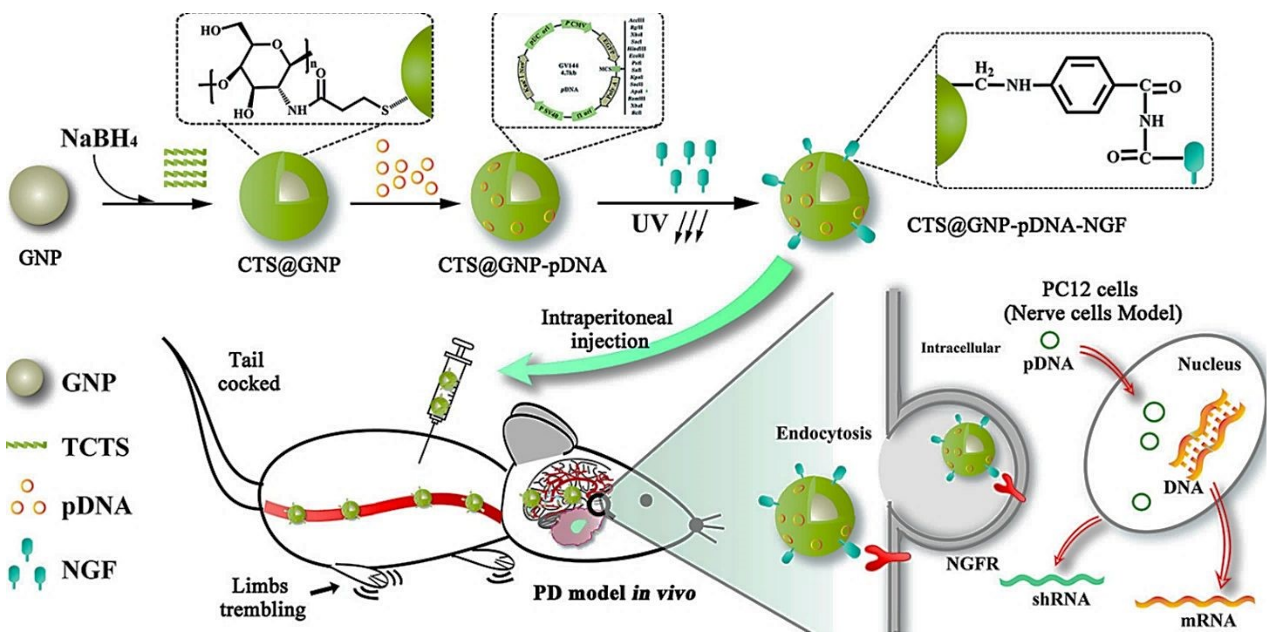

Fig. 7. Schematic illustration for the preparation of the nanocomposite, coating with the pDNA (plasmid DNA) and nerve growth factor (NGF). The NFG-driven endocytosis into PC12 cells was

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followed by inhibited enhanced cellular and dopaminergic neurons proliferation. *In-vivo* model of PD showed BBB permeability and blocking of α-syn overexpression. Adapted from reference [105] with permission from Elsevier, copyright 2018.

AuNPs were exploited as neuronal drug delivery cargo for the most efficient therapies of PD. Nanoflowers of multibranched AuNPs were prepared and acted as transposing carrier of L-DOPA to penetrate the BBB. [106] A novel AuNPs-based platform for the cerebral drug delivery of L-DOPA and DA was developed. The AuNPs surface was functionalized by three different amantadine derivatives due to their ability to bypass the BBB and their biocompatibility. [87], [107],[108] The surface-functionalized AuNPs were compared to polyethylene glycol-coated AuNPs (PEG-AuNPs). L-DOPA or DA were attracted to the AuNPs by several potential surface interactions. The developed systems were investigated in the presence of bovine serum albumin (BSA) as it is the most abundant protein in the body that may form a protein corona hindering the drug's release. Peptidoglycan monomer-AuNPs (PGM-AuNPs) was proved to be the most successful drug delivery tool as it had the highest drug cargo especially from the DA. Additionally, the impact of the BSA on pharmacokinetics and pharmacodynamics was almost diminished. [87] However, neither *in-vitro* assessments nor *in-vivo* studies were performed to further reveal the anti-PD activity and efficiency. AuNPs were reported to be incorporated with other therapeutic agents to exploit the beneficial characters of the AuNPs. For example, it acted as the conductive component in self-healing hydrogel that exerted anti-inflammatory effect. [109] Another hydrogel was also prepared using AuNPs conductive properties to design an injectable implant in the brain for PD treatment. [110] Also, AuNPs acted as a drug carrier for through electrostatic interactions, [87] NIR-responsive, [111] gene carrier and [112] allowing CT imaging. [113] Diverse applications of AuNPs for the treatment of PD are listed in **Table 2.**

Table 2. AuNPs-based PD drug delivery systems, performed biological assessment, outcome and the mechanism of action

Nanoformulation	Size (nm)	Zeta potential (mV)	Biological assessment	Efficacy outcome	Mechanism of action	Ref.
Electroconductive hydrogel using dialdehyde polyurethane as nano-crosslinker, AuNPs (CDAH)	15	-26.2 ± 2.7	*In-vitro* cytotoxicity by neural stem cells *and in-vivo* by oxidopamine (6-OHDA)-induced rat model	CDAH2 hydrogel was found to be biocompatible by quantifying M2/M1 macrophages. The ratio of the CDAH2 group was double the control one. In the *in-vivo* model, there was significant functional recovery	The hydrogel neutralized the ROS production, decrease inflammation of neurons and delay dopaminergic neurons degradation in SNpc, striatum glial fibrillary acidic protein (GFAP+) astrocytes were limited	109
AuNPs-pDNA loaded into liposomes, NGF and docosahexaenoic acid linked to the liposomes surface as targeting ligands to develop AuNPs(pDNA)-Lipo-NGF-DHA	20-40 nm of the AuNPs, increased to 200 nm	-15	Cell viability test of SH-SY5Y cells and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) *in-vivo* model	AuNPs-(pDNA)-Lipo-NGF-DHA significantly enhanced the cell viability relative to the control but not a significant difference compared to AuNPs(pDNA), in PD disease model, TH was increased, improved bradykinesia, improvement in the cognitive impairment and motor dysfunction	AuNPs (pDNA)-Lipo-NGF-DHA conferred protection of the dopaminergic neurons by elevating the TH and constrain the overexpression of α-syn, opposed long-term potentiation (LTP) inhibition	112
AuNCs functionalized with dihydrolipoic acid (DHLA-AuNCs)	1.87 ±0.14	-	Cytotoxicity and microglial protein-inflammatory response on BV2 cells, cytotoxicity, neuronal differentiation and axonal growth assay on N2a cells, *ex-vivo* organotypic brain slice model	Inhibited proinflammation in BV2 cell, improved neurogenesis in N2a cells and in *ex-vivo* brain slice stroke model	Stimulated polarization near to the M2-like phenotype in addition to enhanced anti-oxidant effect and decreased NF-kB signal, prohibited apoptosis that led to enhanced cell viability, limited astrogliosis	94
Hybrid nanoassembly of AuNPs decorated with thiolated amphiphilic β-	150–300 nm, size of AuNPs was 20–	-	Estimation the rate of DA release after the additions of stimulants by CV	Release of 70% of the DA amount through half an hour as the AuNPs@SC16SH/DA	Thiolated-compounds dependent redox responsive drug delivery system for the	114

cyclodextrin incorporated with DA; AuNPs@SC16SH/DA	30 nm			acted as stimuli responsive nanocarrier	DA, β-cyclodextrin acted as carrier for the DA by forming a complex with it, AuNPs allowed the monitoring of the DA release intracellularly followed the penetration of the BBB	
AuNPs coated with brain-targeting exosomes functionalized with rabies viral glycoprotein (RVG)	AuNPs: 48 ±1.5 and AuNPs/exosomes : 105 ±10.1	About -7	*In-vitro* binding efficiency using bEnd.3 mouse brain endothelial cell line, C6 rat glioma cells, or Hela cervical cancer cells, *in-vitro* BBB model using Astrocyte cells and bEnd.3 cells and murine model and *in-vivo* assay to determine the accumulation of the AuNPs/exosomes in the brain	bEnd.3 and C6 displayed the greatest binding affinity towards the AuNPs/exosomes than the Hela cell so the nanoparticles have brain-specific affinity, the AuNPs/exosome crossed the BBB with a significant increase relative to the AuNPs coated with unmodified exosomes, the *in-vivo* model demonstrated intense fluorescence from the brains treated with RVG-exosomes-coated AuNPs	Enhanced BBB permeability of the AuNPs after the coating with brain targeting RVG-protein ligated to exosomes	[115]
L-DOPA-functionalized multi-branched nanoflower-like gold nanoparticles (L-DOPA-AuNF)	90 nm	-34.6 ±1	*In-vitro* test of the L-DOPA-AuNF accumulation in the hCMEC/D3 brain endothelial cells, penetration of L-DOPA-AuNF across the brain endothelial monolayers, internalization of L-DOPA-AuNF into brain macrophages	High intracellular accumulation in the brain endothelial cells in the cytoplasm and the peri-nuclear space, penetration and internalization of L-DOPA-AuNF into the brain microglia without inflammation	Energy-dependent cellular internalization of L-DOPA-AuNF into brain endothelial monolayers and brain microglia due to L-DOPA functionalization and may be due to receptor-independent mechanism	[116], [106]

NIR-responsive PLGA microspheres loaded with pramipexole (PRX) and hollow gold nanospheres (HGNS) (PRX/HGNS MS)	HGNS was 40 nm, PRX/HGNS MS was 24 µm	-	Cytotoxicity assessment using C2C12 myotubes, RAW macrophages, PC12 model neurons and 3T3 fibroblasts, *in-vivo* model including pharmacokinetics, pharmacodynamics and immunohistochemistry	HGNS and PRX/HGNS MS did not exert significant cytotoxicity were found biocompatible, the release rate of PRX from PRX/HGNS MS significantly increased compared to PXR from PXR MS, NIR-exposed mice treated with PRX/HGNS MS exhibited faster improvement relative to non-NIR exposed mice, significant decrease of TH in the striatum	Significant post-treatment elevation if DA, homovanilic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC), protective effect of the neurons conferred by PRX/HGNS MS and NIR-treated mice	111
Self-healing composite hydrogel of O-carboxymethyl chitosan (CMC)OTA@Au (oxidized tannic acid modified gold nanocrosslinker) (COA)	27.79 ± 2.89 nm	-45.6 ±2.7	*In-vitro* antioxidant test by neural stem cells (NSCs) and anti-inflammatory test by J774A.1 murine macrophages, *in-vivo* PD model followed by behavioral and electrophysiological assessment, immunofluorescent and immunohistochemical assays	NSCs proliferation was enhanced in the presence of COA, upregulation of GFAP, β-tubulin and MAP2, about 90% of the inflamed cells were healed after 12 h of COA treatment, inflammatory proteins expression was not expressed in COA-treated macrophages, significant increase in the counterclockwise rotation period, improved forelimbs contact, low spikes count in the projection neurons discharge behavior	The developed COA has efficient self-healing ability and injectability, can enhance the cellular proliferation and subsequent differentiation, can be developed as implant injected to the brain	110

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3.1.2. Silver nanoparticles (AgNPs)-based systems for the treatment of PD

AgNPs are widely distributed to multiple organs. However, it is cleared from all the organs after 8 weeks of the initial exposure except from the testis and remarkably, the brain, as they have the ability to cross the BBB. [117], [118], [119] They were reported to stimulate inflammation, especially in the first 24 h of exposure. [117], [120] However, based on a comparative study, several *in-vitro* assays were comparing biogenically prepared AgNPs and AuNPs by *Acacia auriculiformis* leaves. AgNPs decreased the fluorescence and absorption magnitude in the *in-vitro* assessments in addition to the enhanced anti-oxidant effect. Thus, AgNPs were speculated to have superior inhibitory effect in comparison to the Au counterparts. [121] Gonzalez-Carter et al, proved that the citrate-capped AgNPs-induced immune response enhanced the microglia ability to upregulate anti-inflammatory enzymes and reduce ROS. Following AgNPs microglial internalization, AgNPs induce the expression of cystathionine-γ-lyase (CSE) that detains the release of Ag^+ ions. Also, Ag_2S is formed as a covering layer on the surface of the AgNPs. Consequently, ROS, nitric oxide and TNF-α production are mitigated. From all these findings, it can be concluded that AgNPs suppresses the inflammation and neurotoxicity of the microglia cells. [122]

The green synthesis of AgNPs for the treatment of PD [123–126] and exerting anti-oxidant effect have been previously reported.[127, 128] The plant extract of *Mucuna pruriens* was found to have reduction capability that was exploited to produce AgNPs and simultaneously, containing high L-dopa amounts. [129] Sardjono et al, reported the preparation of AgNPs (36.5 nm) by the seeds extract and performed catalepsy assessment to investigate the efficiency of the prepared NPs in the *in-vivo* model. Gradually increasing doses starting from 5 to 25 mg/kg were tested on 3 months male mice. Groups of mice treated with 5, 10 and 15 mg/kg of AgNPs significantly improved the catalepsy symptoms relative to the control and pure extract-treated groups where the dose of 5 mg/kg-treated group was remarkably the most efficient. [124] Therefore, in order to circumvent the potential toxicity of AgNPs, green synthesis, coating with biocompatible polymers or decorating the surface with neural-cells specific targeting ligands are all potential pathways that should be adopted. [130]

3.1.3. Iron oxide NPs (IONPs)-based systems for the treatment of PD

The application of iron oxide nanoparticles (IONPs) can be adopted through either of two approaches. The first one is through actively targeted therapy. For example, IONPs were coated

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with oleic acid which acted as a cargo and then layered with short hairpin RNA (shRNA). The molecule was endocytosed through NGF-receptors. The developed nanoparticles constrained the expression of α-syn as concluded from the adopted *in-vitro* and *in-vivo* models by PC12 cells and MPTP-bearing mice, respectively. [131] Cheng et al, exploited the NIR-assisted penetration of the BBB to deliver the anti-PD drug; minocycline through loading it into Fe_3O_4 NPs. [132] A theoretical simulation study was performed to design PEGylated Fe_3O_4-based nanocargo as carrier for DA. PEGylated Fe_3O_4 NPs were coated with albumin to enhance the BBB penetrability and were loaded with DA thus, the developed NPs were speculated to provide sustained DA release after the neuronal uptake.[133] Iron oxide NPs coated with curcumin were developed and the results showed rescued DA and norepinephrine levels in addition to the anti-oxidant effect [134]. Ferric ions were coordinated with curcumin and poly(vinylpyrrolidone) (PVP) to develop PVP ultrasmall coordination polymer NPs (Fe-Cur NCPs, 10 nm) that was proven through the *in-vivo* model to alleviate the PD symptoms by improving the mitochondrial stress and having anti-inflammatory effect. [135] The purpose of the study conducted by Moayeri et al., was the replacement of the missing dopaminergic neurons with stem cell therapies that are guided towards specific injury. So, external magnetic field was applied to PD *in-vivo* rat model and the therapeutic effect of superparamagnetic iron oxide nanoparticles (SPION)/poly-L-lysine hydrobromide (PLL) was found to be about 96%. Consequently, the transfection with SPIONs/PLL was found to be successful strategy for the translocation of the stem cells in the target tissue. [136]

The second approach is underpinned on the application of external magnetic field. SPIONs can ameliorate the remedial effect of human mesenchymal stem cells (hMSCs). Dextran-coated IONPs. Both rotational and motor behaviors were significantly improved relative to the control. This improvement was attributed to the enhanced migration of hMSCs towards the damaged DA neurons and their subsequent differentiation to resemble the DA-neurons.[137] To enhance the selectivity of the SPIONs towards PD, the binding affinity of streptavidin (SA) and biotin was exploited. The developed SA/PEI-SPIONs were tested using biotin-treated PC12 cell as an *in-vitro* model. The surface modified-SPIONs demonstrated greater binding the PC12 cells' membrane as observed by TEM. [138]

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3.1.4. Other MNMs-based systems for the treatment of PD

The experiment 6-OHDA-bearing hemiparkinson's mice showed that the release of DA from the implanted DA-loaded TiO_2 lattices improved the motor symptoms for one month and significant reduction of the symptoms was still observed after two months.[139] Interestingly, TiO_2-based implant with nanopores provided sustained release up to 30 days post-implant incorporation.[140] Punitha and coworkers adopted green synthesis pathway to prepare TiO_2 NPs (34 nm) and the cytotoxicity using PC12 cells was in the range of 31.2-62.5 µg/mL.[141] Yet, dose-dependent dopaminergic neural toxicity of TiO_2 was corroborated after accumulation in the midbrain substantia nigra of Balb/c mice. [6]

Selenium NPs (Se NPs) were proven to have neuroprotective effect so were reviewed as potential therapy for CNS diseases as PD. [142] For instance, effect of the Se NPs is attributed to the crucial role of Se to allow the normal function of several peroxidase enzymes [143] and inhibiting inflammatory mediators as TNF-α, Nf_kB and PEG2 [144] to exert its anti-oxidant and anti-inflammatory effects, respectively. Derivatives of aminothiazole were synthesized and used for the development of Se NPs pursuing fortified enhancement of the neurological functions. The molecular docking studies revealed blocking of the *h*MAO isoforms (A and B). Simultaneously, the IC_{50} of the NPs was only 0.033 µM, preceding the normal-sized counterparts' potency by about 70%. In the haloperidol-induced PD *in-vivo* model, the behavioral test results of the NPs group showed improvements and enhanced exploration. Therefore, the Se-based nanoformulation is elicited as effective anti-PD. [145]

Gao et al, developed combined genetic and antioxidant therapy through NIR-stimulated magnesium oxide (MgO)-based nanocomposite; MgOp@PPLP and both *in-vitro* and *in-vivo* assessments results demonstrated enhanced permeability to the BBB in addition to the exerted anti-inflammatory and antioxidant effects. [146]

PD-lesioned cell model by 1-methyl-4-phenylpyridinium (MPP^+) was adopted to reveal the remedial effects of hexagonal boron nitride NPs (hBNs). MTT and LDH showed boosted cells' viability and neural cells protection. Also, hBNs had aggravated defense against destructive oxidants, opposed the MPP^+-induced cellular apoptosis and exerted neural cryoprotection. [147]

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Cerium oxide nanoparticles (CeO_2 NPs) are well-known anti-oxidant materials that resembles the effect of superoxide dismutase and catalase. [148–150] So, the exploiting of the CeO_2 NPs antioxidant properties was pertinent with PD treatment. *Saccharomyces cerevisiae* yeast model of PD was adopted to investigate the effect of CeO_2 NPs. The α-syn expressing yeast cells showed enhanced viability with gradually increasing concentrations of CeO_2 NPs up to 50 $ng.\mu L^{-1}$ due to the accumulation of α-syn in the plasma membrane instead of the cytoplasm as shown by the cell lysate analysis. Also, there was observable diminishing of the mitochondrial impairment and ROS generation. This improvement was thought to be through the surface absorption of the α-syn on CeO_2 NPs which constrained the α-syn fibrillation. [151] Also, several shapes of ceria NPs were investigated and the flower shape had the most powerful anti-oxidant activity. [152]

Although *in-vivo* manganese (Mn) accumulation causes idiopathic PD-resembling symptoms [153], controversial results were obtained from literature. Based on Sharma and coworkers' study, Mn NPs (30-40 nm) showed impairment of the cognition and motor ability of the rats after 8 days of administration. Additionally, definitive brain injuries were detected in multiple regions accompanied by BBB distortion, dissipated blood flow to the brain and cerebral edema.[154] On the other hand, citrate-capped Mn_2O_3 NPs (C- Mn_2O_3 NPs) ameliorated the PD consequences and chelate the excess Mn so, prevents its subsequent neuro-damage. [155] Wang et al, prepared chiral Mn_2O_3 NPs. The *D*-NPs showed enhanced α-syn fibrillation inhibition and anti-oxidant effect driven by electromagnetic field. [156] Additionally, using dopaminergic neural cells; MN9D, PD lesion was developed then treated with NPs of different facets. It was observable the Mn_3O_4 nanorods with (103) facet had high anti-oxidant capacity and diminishing of α-syn in the cerebrospinal fluid as elaborated by the biological assessments. [157]

3.1.5. Polymetallic nanoparticles (nanozymes)-based systems for the treatment of PD

Nanozymes are recently generated nanomaterials class that gained special interest due to its anti-oxidant capacity by scavenging the harmful hydrogen peroxide into oxygen and water. [158], [159] For example, PtCu nanoalloys (NAs) were found to have catalase-like and superoxide dismutase-like activity. Therefore, they were applied to develop anti-oxidant platform for the amelioration of PD. [158], [159] Liu et al., investigated the effect of PtCu NAs and found that they are effective antioxidants. They dissipated the PD through significantly mitigating the level of ROS and α-syn preformed fibrils (PFF) in the adopted *in-vitro* and *in-vivo* models using primary cortical neurons and in PFF-

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treated mice, respectively. [158] The tri-element nanozyme PtCuSe was developed and found to have anti-oxidant effect. PtCuSe nanozymes caused the degradation of hydrogen peroxide and inhibited xanthine oxidase therefore, they have catalytic activity for hydrogen peroxide reduction (CAT) and resembles the action of super oxide dismutase (SOD). The cell viability of SH-SY5Y cells was investigated and the cytotoxic effect of PtCuSe was minute at concentrations below 120 µg/ml and the cellular uptake investigation by laser confocal microscopy showed a great endocytosis of PtCuSe. MPTP-induced PD *in-vivo* model was adopted, and the nanozyme treated groups showed improvement in the locomotor and cognitive functions. [159] **(Fig. 8).**

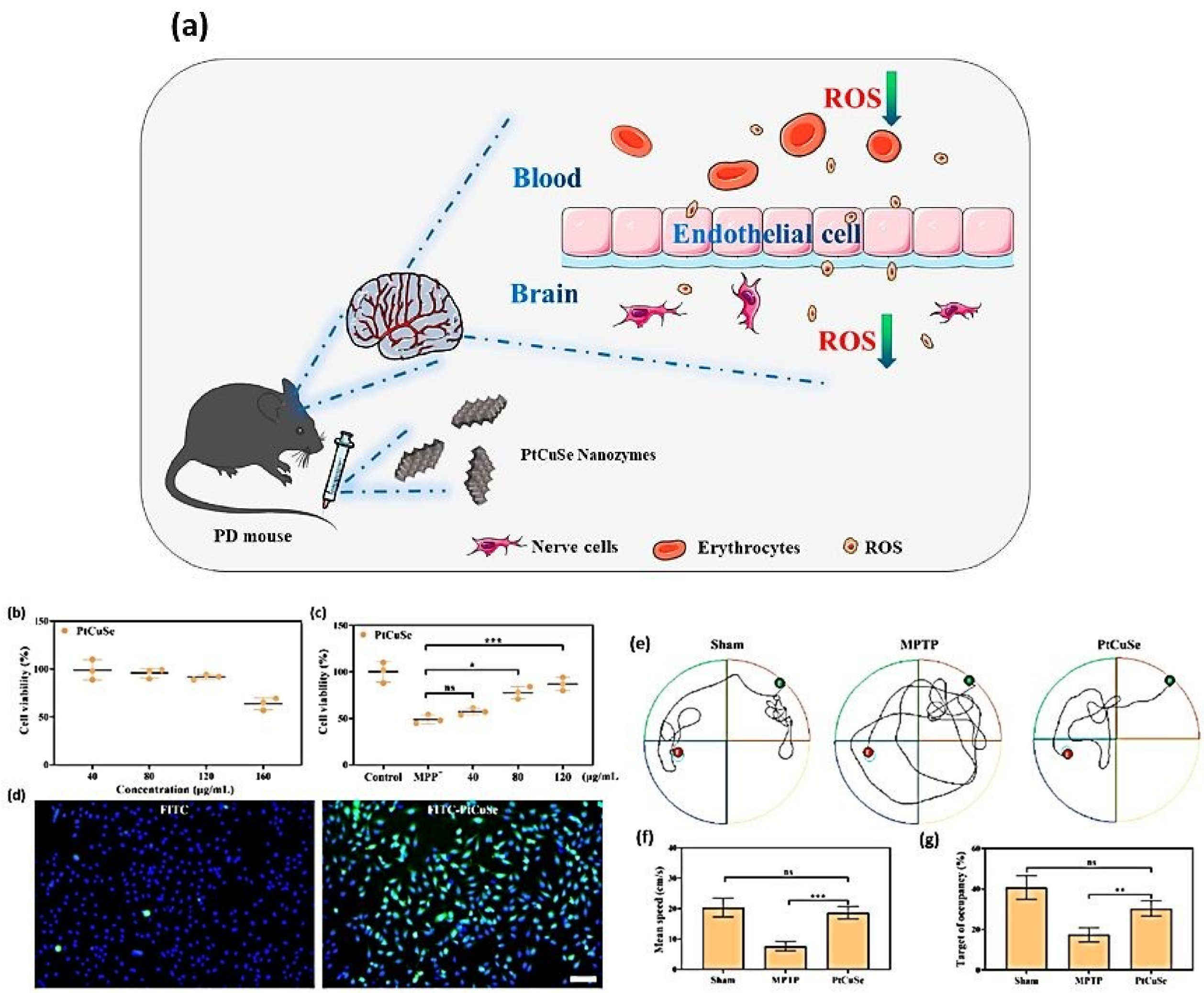

Fig. 8 (a) Scheme of exploiting the antioxidant capability of the nanozyme PtCuSe, **(b)** *in-vitro* cell viability of SH-SY5Y cells after addition of PtCuSe, **(c)** *in-vitro* cell viability of MPP^--treated SH-SY5Y cells after addition of PtCuSe, **(d)** cellular uptake of PtCuSe, **(e)** behavioral assessment

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by Morris water maze test showing the path of mice, (**f** and **g)** the mean time and the relative mean time of the target quadrant. Reproduced from reference [159]

The experiment of chiral $_{L/D}$-Cu_xCo_yS SPs comparison between the two counterparts indicated that the $_{D}$-SPs had preceding ability to prevent the formation of α-syn and disintegrate the already-existing fibrils. This effect was attributed to the capability of $_{D}$-SPs to generate ROS that exert its effect on α-syn.[160] However, the study did not elucidate any off-target harmful effect of the generated ROS or any subsequent neutralizing cascades.

Li et al, formulated nano-bioconjugate/nanozyme of lactoferrin (Lf)-modified Au-Bi_2Se_3 nanodot (ND) (Lf-Au-Bi_2-Se_3). The nanozyme Lf-Au-Bi_2-Se_3 had characteristic protective antioxidant activity resembles that's of SOD, CAT, POD and GPx, a group of enzymes that scavenges the ROS and normalize its level in the normal cells. The catalytic activity of the Au-Bi_2-Se_3 is attributed to two reasons. First, the Au atom can alter the Se atoms within the lattice and replace it with Bi atoms representing defect points. The Bi defect points would enhance the electron transport and consequently, the catalytic effect. [161] Second, the Au atoms would act synergistically by allowing electron transport. [162] Additionally, the LF-surface modification did not affect the catalytic activity of Au-Bi_2-Se_3. To assess the cellular internalization, bEnd.3 cells were used and Lf-Au-Bi_2-Se_3 was found to have great ability to penetrate the BBB. The Morris water maze *in-vivo* model was adopted to assess the treatable effect of Lf-Au-Bi_2-Se_3 and the treated mice exhibited the best intellectual and physical improvement and confirms the pivotal role of Lf in enhancing of the transcytosis in the BBB. Additionally, high levels of tyrosine hydroxylase (TH), healed mitochondria, protected Nissel-positive cells and normalized *ex-vivo* lipid peroxidation were confirmed in the Lf-Au-Bi_2-Se_3-treated group. The biosafety of the Lf-Au-Bi_2-Se_3 was corroborated by the normally functioning main organs. The uptake of the Lf-Au-Bi_2-Se_3 into the brain cells was found to be 2.67 times more than Au-Bi_2-Se_3 which further confirms the ability of the nanorods to penetrate the BBB. Finally, the clearance of Lf-Au-Bi_2-Se_3 was found to be mainly through the urine which is attributed to the enhanced renal infiltration of the tiny-sized nanorods. [88]

4. MNMs-based systems as theranostics for PD

Due to the continuous urge of early accurate detection and effective treatment of PD, researchers invested their efforts to develop theranostic platforms that achieve both goals. Novel

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multifunctional nanoparticles were designed to real-time monitor the disease as well as act as a targeted therapeutic agent like SPIONs. As mentioned earlier, SPIONs are biocompatible and biodegradable contrast agents exploited in MRI and can be manipulated to cross BBB with their tunable sizes and shapes and can be green-synthesized pursing great biocompatibility.[70] Moreover, they can remain circulating in the body allowing for better therapy and can be controlled using external magnetic field. [57,163] For instance, SPIONs-loaded liposomes were used as theranostic agent for image-guided drug delivery in glioma condition, therefore, this formulation can be employed in PD. [164]

Another study was conducted using resveratrol-Fe_3O_4-loaded liposomes for sustained drug release at the target site using external magnetic field. This formulation was guided using MRI to ensure crossing BBB and reaching the target site in PD rat models.[165] Niu et al. investigated the use of magnetic nanoparticles in gene delivery, where they synthesized N-isopropylacrylamide-acrylic acid-functionalized Fe_3O_4 NPs to confer pH and temperature responsiveness. Then, they photo-immobilized nerve growth factor to the NPs along with short hairpin RNA for gene delivery in PD models, however, they did not assess the MRI properties of such NPs. [166] Thus, this multifunctional system can be further implemented in MRI-guided drug and gene delivery in PD cases. Garcia-Pardo et al. also formulated DA-encapsulated iron nanoparticles made of iron metal nodes polymerized using bidentate ligand as bioinspired nanotheranostic agent. It displayed MRI properties, allowed for efficient DA delivery to PD animal models, and proved to be biosafe *in-vivo*. [167]

Switchable nanoparticles for simultaneous drug/gene delivery and CT imaging were developed. The programmed drug delivery system (MBPCS) was composed of levodopa-quinone gold nanoparticles (GNP) integrated with 2 derivatives of Zwitterionic poly-(carboxybetaine)-based curcumin where the last was releasable via a cleavable link in the DA neurons of PD. B6 peptide was linked on the surface of the nanoparticles facilitating their penetration of the BBB. The intracellular internalization was adopted by using mazindol (MA) that binds preferentially to the DA neurons. Following the endosomal/lysosomal escape, the gene delivery phase starts by releasing α-syn gene (SNCA). The GNP and curcumin are then released because of MBPC degradation. GNP interact with Fe^{3+} and quinone groups allowing the CT. [106]

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5. MNMs and BBB penetration

Generally, several BBB penetration mechanisms of the different classes of the nanomaterials were described and reviewed elsewhere.[168] Concerning the MNMs, they can penetrate the BBB either by active or passive pathways. Receptor-mediated endo/transcytosis, adsorption-mediated endocytosis and carrier mediated transport are all examples of the active pathways. On the other hand, the passive pathway involves the passage of the hydrophilic small-sized NPs across the endothelial cells. [168] **(Fig. 9)**. Proteins as nerve growth factor (NGF) [105], [112] poly unsaturated fatty acids as docosahexaenoic acid (DHA)[112] and PGM[87] are all examples of surface functionalizing moieties allowing receptor-mediated endocytosis. [168] Li et al, prepared Au-Bi_2Se_3 nanodots for PD diseases and functionalized the surface with lactoferrin (LF) to enable the active targeting of the BBB through receptor-driven transcytosis. [88] The B6 peptide (CGHKAKGPRK) was used to design switchable AuNPs-based theranostic formulation where the penetration of the BBB was confirmed and the cellular internalization of SH-SY5Y cells was described to be through caveolae and clathrin-driven endocytosis. [113] AuNCs (2.5 ± 1 nm) were investigated, and their penetration of the BBB was proven. The AuNCs were injected intraperitoneally in mice and after 6 h of 20 mg/kg injection, the AuNCs were detected by TEM in the SN sectors in addition to the neurons. [96] Cheng et al, investigated the penetration of an iron-based nanoformulation through an *in-vitro* model and found that the cellular penetration can be through 3 different pathways. [135] Consequently, the MNMs were reported to penetrate the BBB through different mechanisms depending on the sizes and surface properties.

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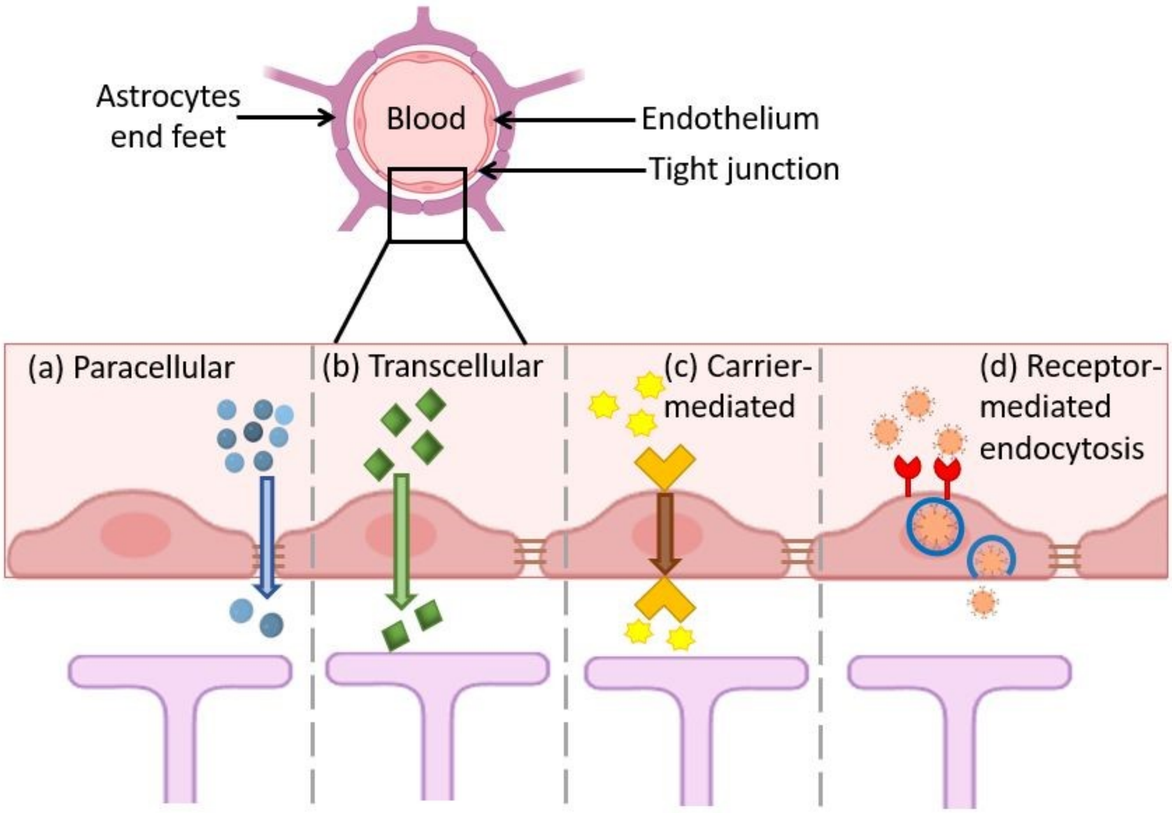

Fig. 9. Mechanisms of BBB penetration by the nanomaterials. Passive pathways include (a) paracellular and transcellular penetration while the active transport pathways include (c) carrier-mediated and (d) receptor-mediated BBB penetration.

6. *Toxicity and biocompatibility of MNMs*

Majorly, the axiomatic transportation of nanomaterials into clinical application is constrained by the inscrutable toxicity effects on the CNS and specifically, the brain. Heavy metals were previously reported to induces neurotoxicity that may resemble the PD-associated manifestation. [169,170] Therefore, the toxicity of the nano-constructed counterparts would be of great importance and pertinent as many of these nanoparticles release metallic ions after *in-vivo* administration. Additionally, the tiny size of the nanostructures permeates their smooth flow across the BBB and distribution within the brain parts remarkably, to the SP which has great importance due to the existence of dopaminergic neurons. [6,171] PD is associated with other physiological alterations such as inflammation, α-syn aggregation and impaired antioxidant response. All these impairments were observable from the exposure to several MNMs. [172,173], [174] For instance, TiO_2 NPs affect the hippocampus, cerebellum and substantia nigra. [175],[6] Certain specific pathways of the TiO_2-induced

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toxicity have been illustrated in literature proving detrimental effect. Wu and Xie conducted a study to investigate the *in-vitro* and *in-vivo* toxicity of TiO_2 adopting PC12 cells and zebrafish embryos, respectively. The results corroborated the presence of neurotoxic effect due to the accumulation of TiO_2 NPs and the generation of ROS. Also, the degradation of the dopaminergic neurons was observable. [176] Also, TiO_2 administration caused electrolyte imbalance and activated inflammatory response by stimulating IL-6 and NF-KB. [177], [178] Moreover, TiO_2 promoted cerebral stimulating the oxidative stress-driven cellular damage by constraining the anti-oxidants factors [179] and elevating the intra-mitochondrial ROS alone or with simultaneous exposure to AgNPs. [180] From other studies, TiO_2 caused the accumulation of α-syn that mitigates the DA in the brain which is a substantial mechanism causing PD. [181],[172], [182]

Despite the remedial effect of green-synthesized zinc oxide NPs (ZnO NPs) [183], other studies reported their cerebral cytotoxicity. [184], [171] A study performed by Jin and coworkers compared the induced cytotoxic effect by several ZnO-based nanostructures. ZnO NPs, long ZnO nanorods (l-ZnO NRs) and short ZnO nanorods (s-ZnO NRs) were prepared and the *in-vitro* assessment was performed using human neuroblastoma cells SH-SY5Y and revealed that l-ZnO NPs had the least toxicity (LD50 = 17 µg/ml). Several concentrations of l-ZnO NPs were tested using zebrafish larvae *in-vivo* model. From the investigation of the brain, l-ZnO NRs high doses stimulated the ROD production that consequently, sequestered the motor ability and neurons development, disruption of dopaminergic neurons and cerebral apoptosis coherently leading to PD-resembling manifestations. [184] The toxicity of the Zn^{2+} ions from ZnO NPs was investigated through *in-vitro* and *in-vivo* assessments. The cell viability of the glial cells A172 was greatly decreased after 1 day of exposure and DNA damage was observable after only 3h as confirmed by comet assay. The zebrafish embryos were exposed to gradient concentrations of ZnO NPs. After 96 hours post-fertilization (hpf), locomotor impairment was resulted suggesting the possible role of the released Zn^{2+}. The cytotoxicity and genotoxicity were believed to be caused by enhanced ROS production. Additionally, the locomotor disorder was not elucidated explicitly but attributed to dopaminergic cells destruction and therefore, affecting the muscles and nerves (**Fig. 10).** [185] **Table 3** summarizes some PD-related toxicities associated with MNMs exposure.

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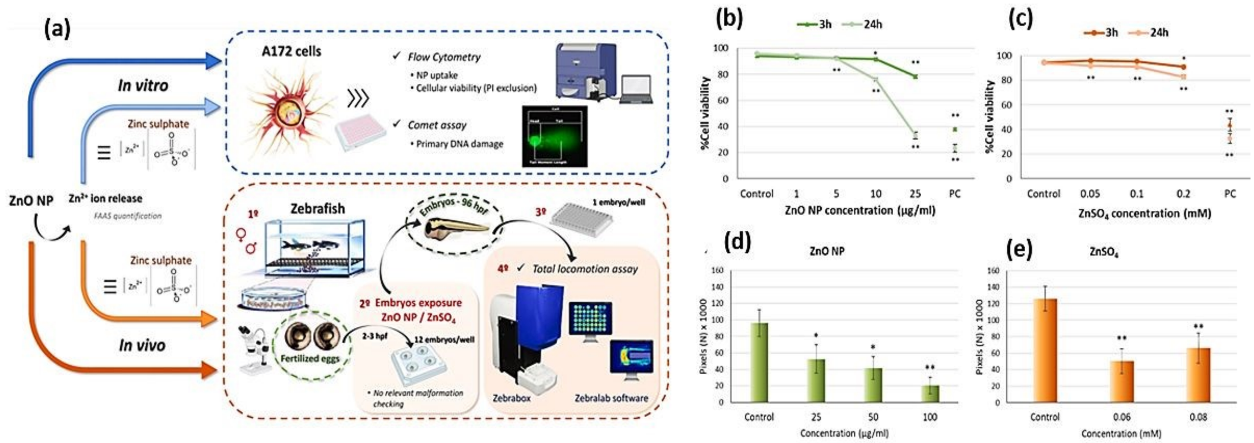

Fig. 10. (a) Schematic illustration of the prepared ZnO NPs and the effect of the released Zn^{2+} ions on A172 cells and the adopted *in-vivo* model using zebrafish embryos, **(b and c)** *in-vitro* cell viability assessment of A172 compared to $ZnSO_4$, **(d and e)** locomotor impairment of zebrafish embryos after exposure to ZnO NPs and $ZnSO_4$. Adapted from reference [185] with permission from Elsevier, copyright 2024.

Table 3. Several MNMs' exposure duration and the resulting neurotoxicity

Type & size of NPs	Exposure duration	Biocompatibility & Toxicity	Ref.
Fe_3O_4, about 10 nm	24 h	Neuro-destructive effect through oxidative stress. Interaction between the iron and DA may induce neurons toxicity by generating toxic products. The aggregated α-syn can cause accretion of the iron level that leads to generation of OH destructive radicals.	186 187 188 189
Ag NPs, less than 100 nm	28 days	Induced neuronal apoptosis and cellular degeneration known as dark neurons due to ROS production and exaggerated inflammatory response.	190
Co NPs, less than 100 nm	24 h and 6 days	Destructive oxidative stress evidenced by the depletion of GSH, neurotoxicity due to calcium homeostasis and lipid peroxidation. Also, mitochondrial swelling and structures that resembles fibrosis were notable, leading to ferroptosis-like cell death.	191
CuO NPs, 50 nm	60 and 120 h	α-syn aggregates, promote pertinent cellular cytotoxicity	192
CuS NPs, 77.89 nm	24 h	Cytotoxic effect at low concentration, caused developmental neurotoxicity	193 194
NiO NPs, 50 nm	24 h	Altered the fibrillation kinetics of α-syn, enhanced ROS production due to the alleviated defensive pathways and the enhanced inflammatory mediators' expression	195

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Long ZnO nanorods (l-ZnO NRs), diamter: 159.3 ± 17.9 nm and length: 1.1 ± 0.15 µm	24-144 h post fertilization (hpf)	High doses stimulated the ROD production, sequestered the motor ability and neurons development, disruption of dopaminergic neurons and cerebral apoptosis leading to PD-resembling manifestations	184

7. Challenges and future perspectives

The bridling of clinical improvement in the journey of PD starting from the detection to treatment is attributed to the lacunae that can be recapitulated as long-time of asymptomatic period, absence of sharply definitive biomarker, heterogenous nature of the disease, dearth of effective treatment and resistance development. The use of MNMs represents a promising but complex avenue for addressing these issues. While NPs have shown potential in enhancing detection through sensitive biosensors and improving therapeutic delivery, challenges persist. These include ensuring biocompatibility and stability in biological systems, achieving precise targeting to diseased cells, and avoiding off-target effects.[48] The encapsulation of the MNMs into emulsions would provide prolonged drug release. Also, the design of the carrier medium to be NIR-responsive would confer more specific release in the target cells/sites.[111] The incorporation of the MNMs into biocompatible nanoshells [196] or porous nanocarriers would add a protective shield from pre-mature *in-vivo* degradation. Moreover, the surface modification of the MNMs with targeting ligands would enhance the on-site neurons-specific drug release [88, 197]. The exploiting of specific BBB-transporters would also enhance the cerebral drug delivery surface modification of the MNMs by ligands specific to these receptor, reviewed by Mhaske et al.[198] Furthermore, scaling up from laboratory success to clinical application involves overcoming significant hurdles in manufacturing and regulatory approval. Concerning the MNMs, the design of a formulation for PD therapy or *in-vivo* detection as imaging would require prolonged testing to ensure the safety during the use and subsequent complete clearance from the body. Additionally, challenging of animal models reciprocation, ethical issues about human samples and the ambiguity to provide clear mechanistic molecular pathways of aging and neurodegenerative diseases, particularly PD, are all insistent issues that need to be addressed. [199,200] Future research should focus on refining nanoparticle technologies to enhance their specificity, reduce potential toxicity, and improve targeting mechanisms. Advancements in AI and machine learning could further aid in analyzing data from nanoparticle-based detection and therapies, leading to more personalized and effective

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treatment strategies. Addressing these challenges through innovative approaches in biomarker discovery, model development, and therapeutic applications will be crucial for advancing clinical outcomes and improving the quality of life for individuals with PD.

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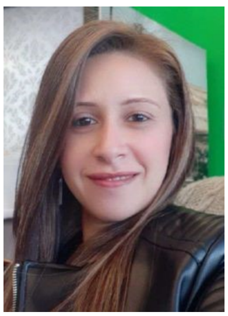
Biographies



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Data Availability Statement:

This review article does not contain original data. All data referenced in this article are from published studies and sources cited in the reference list. Additional information can be obtained from these sources as noted.