



MOF and COF-based drug delivery system for Parkinson's disease: Mechanism, future and development of artificial intelligence



Chunyue Shi^{a,1}, Yan Liang^{b,1}, Yusheng Wang^{b,1}, Xinyi Zhang^{b,1}, Aparna Kushwaha^{c,1}, Abhinav Kumar^{c,*}, Jun Wang^d, Qin Ouyang^{e,**}, Yong Huang^{b,***}

^a School of Environmental Science and Engineering, Shandong Agriculture and Engineering University, Jinan, 250100, China

^b Dongguan Key Laboratory of Drug Design and Formulation Technology, School of Pharmacy, Guangdong Medical University, Dongguan, 523808, China

^c Department of Chemistry, Faculty of Science, University of Lucknow, Lucknow, 226 007, India

^d School of Chemistry and Environmental Engineering, Sichuan University of Science & Engineering, Zigong, 643000, China

^e Department of General Surgery, Dalang Hospital, Dongguan, Guangdong, China

ARTICLE INFO

Keywords:

Metal organic framework
Covalent organic framework
Parkinson's disease
Drug delivery
Artificial intelligence

ABSTRACT

Parkinson's disease (PD), a progressive neurodegenerative disorder, is plagued by urgent challenges including delayed early diagnosis and limited therapeutic efficacy, with core bottlenecks rooted in its complicated pathogenesis and the limitations of existing technologies. This review highlights emerging strategies that integrate advanced functional materials particularly metal–organic frameworks (MOFs) and covalent organic frameworks (COFs) with artificial intelligence (AI) to address critical gaps in PD management. MOFs and COFs, endowed with precisely tunable pore architectures, high surface areas, and versatile chemical functionalities, offer exceptional platforms for the ultrasensitive detection of PD biomarkers, such as α -synuclein, dopamine, and oxidative stress indicators, as well as for the controlled and targeted delivery of neuroprotective and disease-modifying therapeutics. In parallel, AI technology enables precise optimization of MOF/COF carriers through prodromal symptom identification, drug target discovery, and predictive modeling. Their synergy constructs an integrated “material hardware + intelligent software” system, significantly enhancing the accuracy of early PD diagnosis and the level of personalized treatment. By examining the synergistic interplay between these porous materials and AI methodologies, this review underscores their transformative potential in advancing the early diagnosis, monitoring, and personalized treatment of PD, while critically outlining the key translational challenges ranging from biosafety and large-scale synthesis to regulatory validation that must be overcome to realize their clinical impact.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder that exerts a profound clinical and societal burden worldwide. Pathologically, PD is defined by the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta, accompanied by depigmentation of the substantia nigra and locus caeruleus and the accumulation of misfolded α -synuclein aggregates [1]. These pathological alterations impair dopaminergic neurotransmission within the basal

ganglia, producing the characteristic motor deficits of bradykinesia, rigidity, and resting tremor, alongside diverse non-motor symptoms. A central challenge is that these manifestations emerge only after substantial neuronal loss, limiting the therapeutic window for neuroprotective interventions. This underscores the urgent need for reliable strategies enabling early detection and targeted intervention (see Tables 1 and 2, Fig. 1).

Current diagnostic methods combine clinical evaluation with neuroimaging and biochemical assays. Among these, quantification of

* Corresponding author.

** Corresponding author.

*** Corresponding author.

E-mail addresses: abhinavmarshal@gmail.com, kumar_abhinav@lkouniv.ac.in (A. Kumar), ouyangqin8@sina.com (Q. Ouyang), huangyong@gdmu.edu.cn (Y. Huang).

¹ These authors have the equal contributions.

dopamine (DA) and its metabolites in cerebrospinal fluid and urine is widely employed. Techniques such as high-performance liquid chromatography (HPLC) and capillary electrophoresis offer quantitative accuracy but are restricted by technical complexity and low adaptability for routine clinical practice. Emerging electrochemical and fluorescence-based probes achieve higher sensitivity and selectivity for DA, yet their translation into standardized diagnostic workflows remains limited [1]. This diagnostic gap has motivated increasing interest in advanced functional materials that can bridge sensitivity, specificity, and clinical usability.

Within this context, Metal–Organic Frameworks (MOFs) have emerged as a versatile class of crystalline porous materials capable of addressing several unmet needs in PD theranostics. Constructed from metal ion clusters linked by organic ligands, MOFs exhibit exceptionally high surface areas, tunable pore dimensions, and chemically modular frameworks [2]. These attributes confer distinct advantages for encapsulation of therapeutic molecules, controlled release, and integration with imaging or sensing modalities. Recent reports demonstrate that MOFs can be engineered to simultaneously stabilize neuroprotective agents and detect PD-related biomarkers, thereby providing multifunctional theranostic platforms. Moreover, their structural responsiveness to pH, redox state, or enzymatic activity allows for spatiotemporally controlled release, an especially desirable property for maintaining dopaminergic balance. Importantly, when coupled with artificial intelligence (AI)-driven modelling, MOF-based systems can be systematically optimized for stability, pharmacokinetics, and patient-specific therapeutic profiles [2].

Parallel to these developments, Covalent Organic Frameworks (COFs) have attracted attention as complementary materials with

distinct structural advantages. Unlike MOFs, COFs are assembled from light elements linked via strong covalent bonds, yielding highly crystalline, chemically robust frameworks with ordered porosity [3,4]. Their extended π -conjugation imparts electrical conductivity, which is particularly advantageous for electrochemical sensing of PD biomarkers such as DA and α -synuclein. Furthermore, COFs have been exploited as carriers for sustained drug release, offering superior stability compared to many polymeric systems. Despite these advantages, the translational application of MOFs and COFs continues to face challenges, including cytotoxicity risks, instability under physiological conditions, and barriers to large-scale synthesis. Addressing these issues through rational framework design, incorporation of biocompatible composites, and scalable synthesis protocols is a key focus of ongoing research.

MOFs and COFs, considered complementary families of porous crystalline solids, present different performance profiles arising from their contrasting chemical architectures and bonding features. These intrinsic differences govern their suitability for PD related diagnostic and therapeutic strategies. MOFs rely on metal node to linker coordination that generates variable pore networks, numerous metal based binding sites, and responsiveness to pH or biomolecular triggers. These attributes support high payload capacity for PD active molecules of diverse sizes along with tunable release kinetics, although instability toward water or reactive species can limit practical implementation. Electrochemical and charge transport behavior also emerges from the interaction of metal centers with functional groups embedded in the MOF lattice [122–124]. COFs originate from covalent coupling of organic building blocks, and their robustness is largely determined by the strength and reversibility of the covalent linkages. COFs typically demonstrate more uniform pore size distribution and enhanced

Table 1
Porous materials-based sensors developed for direct PD detection.

Porous material-based biosensors	Target	Sensory mechanism	Sample type	Selectivity and/or Sensitivity	Ref
β -cyclodextrin/Ni-MOF/glassy carbon electrode	Dopamine (DA)	Electrochemical	human serum and dopamine hydrochloride injection samples containing DA	0.7–310.2 μ M; 0.227 μ M	[15]
PCN-222(Fe) ZIF-8/GO	Levodopa (L-dopa)	Electrochemical	Human urine	2 nmol L ⁻¹	[16]
Au/RP1/Ni ₃ HHTP ₂	Levodopa (L-dopa)	Electrochemical	sweat	0.45 μ M	[17]
UIO-66-NH ₂	dopamine (DA)	Electrochemical	mouse brains	1 nM	[18]
The detection of multiple MNTs including DA, Adr, NE and 5-HT.		Electrochemical	PC12 and C6 cells	1.5 nM, 4 nM (Adr), 8 nM (NE), 7 nM (5-HT)	[23]
CuO/C/Ti ₃ C ₂ T	Dopamine (DA), ascorbic acid (AA), and uric acid (UA)	Electrochemical	Human serum	6.718 μ M (DA), 3.035 μ M (AA), and 1.747 nM (UA)	[26]
MIL-101 (Fe) MOF/FC/ILCPE	Glutathione (GSH)	Electrochemical	human urine and hemolyzed erythrocyte	0.15 μ M	[32]
Ni-Zn-MOF/GO/FC/CPE	Glutathione (GSH)	Electrochemical	human blood, GSH tablet and urine	0.003 μ M.	[23]
AuNPs@Cu-MOFs/ITO CDs-MnO ₂ NSs platform Eu(pzdc)(Hpzdc)(H ₂ O) _n (ECP)	alpha synuclein (α -syn) oligomer	electrochemiluminescent (ECL)	human serum	0.42 or 0.38 fM	[24]
	Dopamine (DA)	Photoluminescence probes	DA injections	100 nM.	[25]
	Dopamine (DA)	Fluorescence probe	clinical	21 nM	[46]
Eu- α -cyclodextrin (CD)	Dopamine (DA)	Fluorescence probe	urine from Parkinson's patients.	0.65 nM	[116]
ZGC/ZIF-8-NH ₂ Tb-MOF@PtAptamer {[Cu(Cdcbp)(bipy)] _n Hg ²⁺ , biothiols}	Dopamine (DA) α -synuclein (α -Syn)	Fluorescence probe Fluorescence “turn-on” strategy	urine Fecal	95.3–108.7 % 0.04 pg/mL	[27] [28]
		fluorescence “off-on-off” mechanism.	normal human serum	3.0, 14.2, 15.1 and 8.0	[29]
Eu-MOF	Tryptophan (Trp), Cu ²⁺	Fluorescence probe	pH = 7.4	0.22 μ M and 0.09 μ M.	[30]
Tri-FMIPs	Homovanillic acid (HVA)	Fluorescence probe	serum and urine	The detection limit of 34 nM	[31]
1’@PVDF-PVP	Neonicotinoid insecticide dinotefuran and anti-Parkinson's drug entacapone	photoluminescence	human serum, urine and dinotefuran in real soil, rice, honey	2.3 and 7.6 nM	[32]
MIL-88A (Fe)	Levodopa (L-3,4-dihydroxyphenylalanine)	colorimetric	human urine(10-fold dilution)	7.0 mM	[33]
Zn-CTF/I	Acetylcholinesterase (AChE)	Dual-mode colorimetric/photothermal sensing	human serum (100-fold dilution)	0.003 U L ⁻¹	[34]
Cu-MOF@Ag	Nitrated α -syn (nitro- α -syn)	Combining colorimetric and electrochemical	healthy individuals and PD sufferers	0.5 ng/mL	[35]

chemical stability, particularly in aqueous and physiological environments. These characteristics make them promising for prolonged drug administration and in-vivo biological sensing applications [122–125].

The nature and strength of host–guest contacts within MOFs and COFs critically dictate payload uptake, release behaviour, and biomolecular recognition performance. In MOFs, binding arises from metal centered coordination, aromatic stacking between linkers, and electrostatic attractions, facilitating sequestration of diverse therapeutic agents. COFs, by comparison, depend predominantly on extended π stacking and hydrophobic affinity imparted by their conjugated frameworks, while their rigid channels impose spatial confinement that enables finely regulated release dynamics [122–125]. Consequently, MOFs offer pronounced loading capacity and stimulus guided responsiveness, whereas COFs provide ordered encapsulation and prolonged delivery, establishing a complementary functional balance across the two material platforms.

In parallel with advances in materials chemistry, artificial intelligence technologies are reshaping the research and clinical landscape of PD. Machine learning and deep learning algorithms are increasingly applied to complex, multimodal datasets including speech profiles, gait dynamics, and fine-motor kinematics yielding diagnostic accuracies that surpass traditional clinical assessments [5,6]. Beyond diagnosis, AI is accelerating drug discovery by predicting molecular targets, screening compound libraries, and identifying repositioning opportunities, thereby addressing the high costs and low success rates associated with conventional pipelines. For MOF- and COF-based platforms, AI introduces additional opportunities: predicting host–guest interactions, optimizing framework stability in biological environments, and guiding rational drug–carrier compatibility design. Nevertheless, limitations such as non-standardized datasets, limited cross-population generalizability, and interpretability concerns remain obstacles to clinical implementation. Progress will depend on the creation of curated datasets, development of transparent algorithms, and robust clinical validation (Fig. 2).

Taken together, these developments illustrate the convergence of materials science and computational intelligence in redefining the landscape of PD research. This review critically evaluates the applications of MOFs, COFs, and AI in PD management, highlighting their complementary strengths and intersecting roles in advancing biosensing, therapeutic delivery, and diagnostic precision. By situating porous framework materials within an AI-augmented paradigm, we emphasize how interdisciplinary innovation may ultimately enable earlier intervention, more precise therapies, and improved patient outcomes in PD.

2. Innovative applications of MOF in PD

Metal–Organic Frameworks (MOFs) are a versatile class of porous crystalline materials constructed through the self-assembly of metal ions or clusters with organic ligands. Representative families such as the ZIF,

MIL, and UiO series exemplify the structural diversity achievable within this class, offering tunable pore architectures, exceptionally high surface areas, and multifunctional properties. Importantly, many MOFs derived from biocompatible metal centers (e.g., Zn, Fe, Zr) and physiologically benign ligands exhibit low cytotoxicity, thereby providing a strong foundation for their translation into biomedical applications [7].

In recent years, MOFs have been extensively investigated as high-performance platforms for biosensing. Their ordered porosity, large specific surface area, and framework design flexibility allow precise control over analyte–host interactions, while their inherent ability to incorporate luminescent centers or redox-active sites enables excellent signal transduction. As a result, MOFs have been successfully engineered into fluorescent and electrochemical probes with remarkable signal amplification capacity [8]. Such properties render them particularly attractive for the early diagnosis of PD, where ultra-sensitive and selective detection of trace-level biomarkers is essential.

Beyond diagnostics, the scope of MOF applications has expanded into therapeutic strategies for PD. Owing to their modularity, MOFs can function as nanocarriers for targeted delivery of neuroprotective agents, including metal ions that restore neuronal homeostasis. Furthermore, catalytic MOFs with intrinsic enzyme-mimicking activity (nanozymes) have demonstrated efficacy in scavenging excessive reactive oxygen species and modulating neuroinflammatory responses—two pathological hallmarks of PD. These advances highlight MOFs as a promising multifunctional platform, capable of integrating both diagnostic and therapeutic modalities for innovative management of PD.

2.1. Highly sensitive biological sensing platform

The early and accurate diagnosis of PD is of paramount importance for improving clinical outcomes, as timely identification of the disorder allows earlier therapeutic intervention and better management of cognitive decline. Achieving this goal requires analytical tools capable of detecting disease-related biomarkers at very low concentrations in complex biological fluids with high selectivity and reproducibility. However, conventional approaches such as immunoassays and chromatographic techniques, while reliable in principle, are often hindered by cumbersome sample preparation, high operational costs, and insufficient sensitivity for trace-level analytes. These limitations greatly restrict their widespread application in routine clinical diagnostics [9].

In this context, MOFs have attracted increasing attention as next-generation biosensing platforms due to their unique structural and physicochemical characteristics. The exceptionally high surface area of MOFs provides abundant adsorption sites for target analytes, effectively increasing local concentrations and thereby enhancing detection sensitivity. Their well-defined and tunable pore architectures allow molecular sieving, which facilitates the selective recognition of biomarkers against interfering species commonly present in biological samples. Furthermore, the chemical modularity of MOFs enables facile functionalization with recognition elements such as antibodies, aptamers, or

Table 2

The applications of COFs in the treatment of PD.

Strategies	Material	Treatment Direction	Achievement	Ref
Smart sensing and monitoring	Carbon fiber microelectrode modified by TpPaCOF	Early diagnosis, stage of PD and optimization of levodopa treatment effect	Real-time quantification of dopamine (DA) concentration in the brain, detection limit as low as 8.2 nM, excluding ascorbic acid, uric acid and other interference	[3, 59]
Smart sensing and monitoring	AgCo/TAPB-DMTP-COF	Levodopa ultrasensitive detection	COF high specific surface area ($2385\text{ m}^2/\text{g}$) and AgCoNPs excellent conductivity, electrocatalytic activity	[17, 63]
targeted drug delivery	COF Material Modified with RVG Peptide	Targeted delivery of levodopa, blood-brain barrier penetration	Surface-modified RVG peptide can bind BBB endothelial cell receptor to cross BBB and increase brain drug concentration	[60, 62]
Vector optimization for cell or gene therapy	imine-based COF material	α -synuclein aggregation inhibition	α -synuclein monomer/oligomer is adsorbed by porous structure and large specific surface area, preventing it from forming filament and Lewy body	[74, 77]
Vector optimization for cell or gene therapy	Cationic COF nanoparticles (COFNPs and Ab monomers)	Gene therapy for PD(gene delivery)	Delivery of siPD-L1 can reduce PD-L1-related mRNA expression in CT26 cells by about 60 %, achieving effective gene delivery and expression silencing	[58, 78]

catalytic moieties, greatly expanding their versatility.

Further, MOFs possess intrinsic optical and electroactive properties that make them highly compatible with modern signal transduction strategies. For instance, MOF-based fluorescent probes can achieve ratiometric or turn-on/off responses, while electrochemical MOF composites can amplify redox signals with high stability. Such integrations of MOFs with electrochemical and fluorescence readout mechanisms have demonstrated remarkable improvements in both sensitivity and selectivity compared to traditional materials [10]. Collectively, these attributes position MOFs as a powerful platform for the design of advanced biosensors, capable of achieving the early and precise detection of biomarkers relevant to PD.

2.1.1. Electrochemistry

Accurate quantification of neurotransmitters such as dopamine (DA) and levodopa is fundamental to both the diagnosis and ongoing management of PD [11]. Classical analytical techniques, including high-performance liquid chromatography (HPLC) and enzyme-linked immunosorbent assays (ELISA), provide reliable measurements, yet their high cost, time-consuming protocols, and need for sophisticated instrumentation limit routine clinical use [12]. Electrochemical methods, by contrast, offer high sensitivity, fast response times, and compatibility with portable formats, making them promising for rapid clinical diagnostics. Nevertheless, challenges such as the high oxidation potential of DA and low current response in complex samples have restricted their sensitivity and selectivity [13,14].

MOFs have been introduced as promising building blocks for electrochemical sensor platforms. Their exceptionally high surface area, tunable porosity, and rich active sites can substantially enhance analyte capture and catalytic activity [10]. However, their intrinsically poor electrical conductivity reduces efficiency in standalone applications. To overcome this, researchers have pursued composite strategies that integrate MOFs with conductive materials such as carbon nanotubes,

graphene, conductive polymers, and MXenes. These hybrids retain the porosity and recognition capability of MOFs while significantly improving charge transfer. Such advances have transformed MOF-based sensors from single-target laboratory tools to multi-analyte platforms and wearable technologies, widening their prospects for PD diagnostics.

Several notable studies highlight these developments. Chen and co-workers fabricated a dopamine sensor by coupling nickel-based MOFs with β -cyclodextrin. The hydrophobic cavity of β -cyclodextrin selectively recognized DA, while the Ni-MOF framework contributed porosity and electrocatalytic activity. The device achieved a broad linear range of 0.7–310.2 μM with a low detection threshold of 0.227 μM , effectively spanning physiological and pathological DA concentrations. Recovery values in human serum and pharmaceutical samples ranged from 94.3 % to 102.3 %, underscoring practical reliability. This study illustrates how synergistic integration of molecular recognition with MOF catalysis can enhance selectivity and anti-interference capacity [15].

In another approach, Chen et al. combined polythiophene derivatives with the porphyrinic MOF PCN-222(Fe), generating a PMeTh@PCN-222(Fe) core–shell composite. This sensor detected levodopa at nanomolar levels, with a detection limit of 2 nM and a linear working range of 0.05–100 μM . The system retained over 90 % activity after 30 days and demonstrated stability through 120 repeated cycles, while resisting interference from uric acid. By integrating conductive polymers into porphyrinic MOFs, this work broadened the scope of trace biomarker detection and reinforced the value of hybrid composites in biological analysis [16].

Wearable sensing has also been explored. Xiao et al. reported a ZIF-8/graphene oxide hybrid loaded with tyrosinase, enabling non-invasive monitoring of levodopa in sweat. The platform delivered a linear range of 1–95 μM with a detection limit of 0.45 μM . By integrating wireless electronics, the sensor enabled smartphone-based data transmission for real-time monitoring. This approach provides a significant advance in long-term management of PD by enabling continuous, non-invasive drug

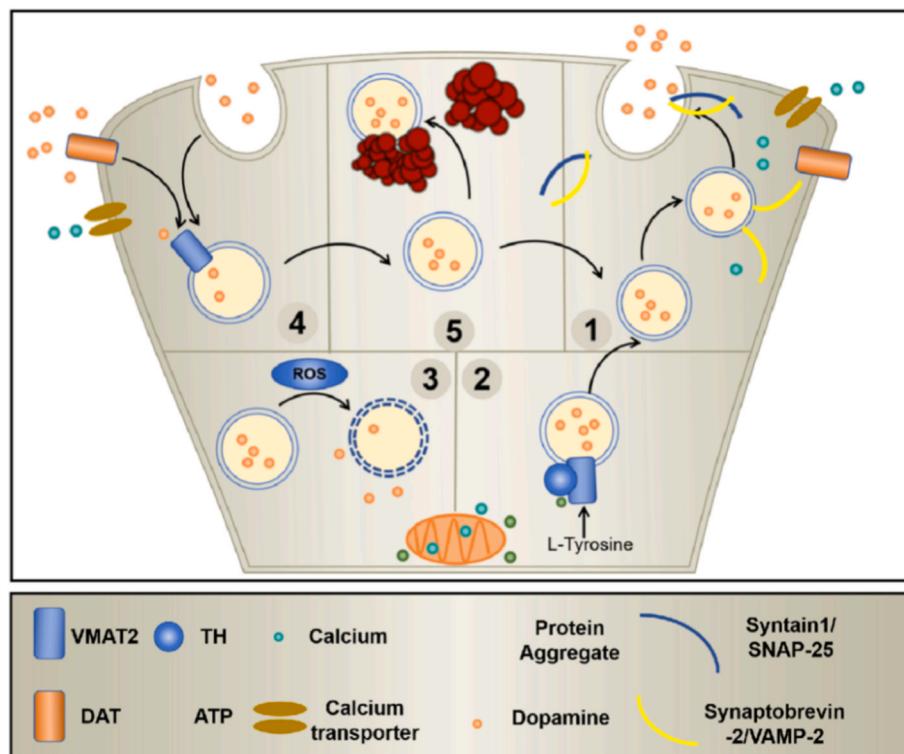


Fig. 1. Intrinsic presynaptic pathways contributing to impaired dopamine release in PD models. Multiple disruptions can compromise DA transmission, including: (1) alterations in the exocytotic machinery such as SNARE-mediated vesicle fusion, (2) reduced dopamine synthesis, vesicular packaging via VMAT2, and delivery to active zones, (3) degeneration of the synaptic vesicle reservoir, (4) defective recycling processes encompassing endocytosis, SV turnover, and dopamine reuptake through DAT, and (5) aggregation of misfolded proteins.

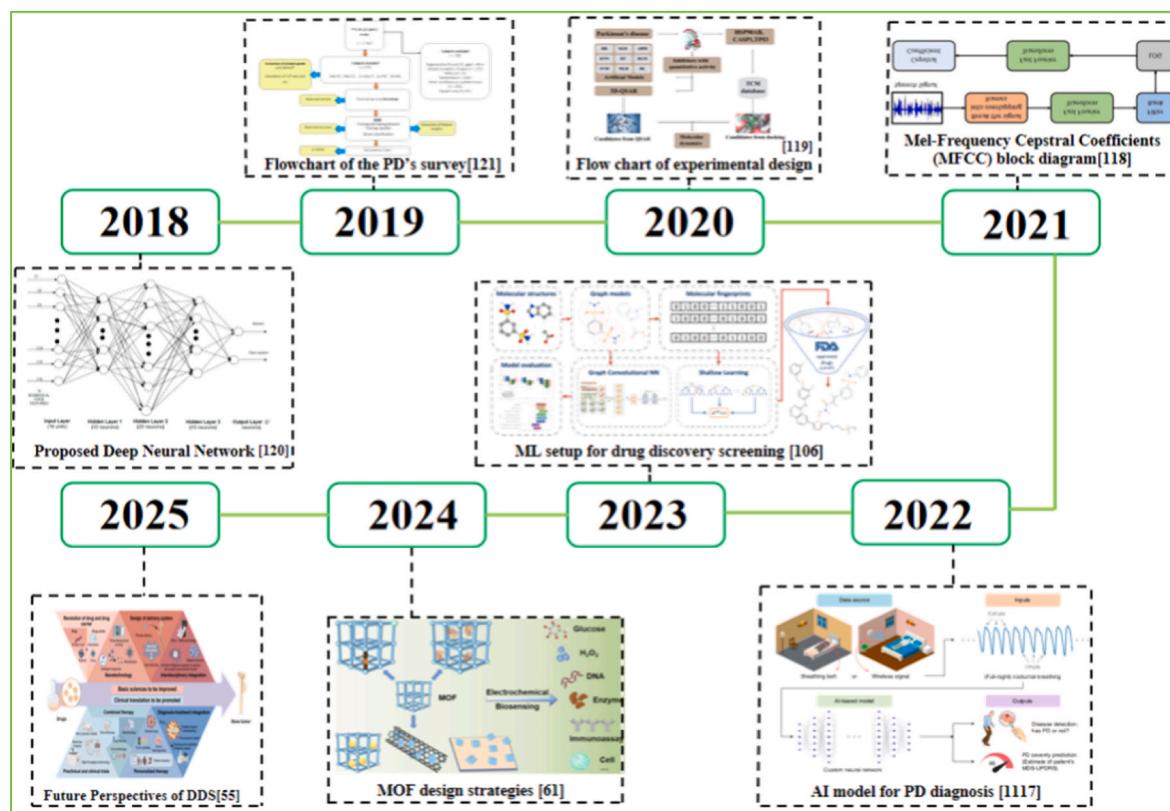


Fig. 2. A timeline showing the recent development of AI in PD treatment.

level monitoring to optimize treatment regimens [17].

Wang et al. advanced *in vivo* sensing through the development of a conductive MOF microelectrode functionalized with conjugated molecular wires (RP1). The RP1 molecules reduced the Gibbs free energy of DA oxidation, accelerating electron transfer and enabling nanomolar sensitivity (linear range 4 nM–0.4 μM; detection limit 1 nM). Applied in PD model mice, the sensor tracked DA fluctuations and uncovered dose-dependent effects of uric acid, which was neuroprotective at low doses but inhibitory at higher levels. Beyond advancing electrochemical detection, this work provided mechanistic insights into disease pathophysiology [18].

Addressing conductivity limitations, Su and colleagues constructed a composite sensor by integrating multi-walled carbon nanotubes with amino-functionalized UiO-66-NH₂. This enabled simultaneous detection of four monoamine neurotransmitters: dopamine, epinephrine, norepinephrine, and serotonin. The platform exhibited high sensitivity, strong biocompatibility, and could monitor neurotransmitter release from stimulated PC12 and C6 cells. Such multiplexing capabilities provide a powerful means to study neurotransmitter dysregulation in PD, which often involves multiple pathways [19]. Amarnath et al. expanded the scope further by synthesizing CuO/C/MXene nanosheets through thermal decomposition of MOF precursors. Their device enabled wide-range detection of DA, ascorbic acid, and uric acid, with detection limits of 6.718 μM, 3.035 μM, and 1.747 nM, respectively. A peak separation of 194 mV between DA and UA ensured strong selectivity even in complex matrices. Such dual-mode platforms are highly relevant for monitoring comorbid conditions alongside PD [20].

Because oxidative stress plays a central role in PD, monitoring antioxidant biomarkers is also critical. Glutathione (GSH), the predominant antioxidant in the brain, is often depleted in PD progression [21]. Rezaiezadeh et al. engineered a MIL-101(Fe)-based carbon paste electrode modified with ionic liquid for ferrocyanide-mediated GSH detection. The device offered a linear range of 0.5–385 μM with a detection limit of 0.15 μM and achieved recoveries of 96.6–102.9 % in

urine and hemolyzed red blood cells, confirming clinical utility [22]. Similarly, Zaimbashi et al. created a Ni-Zn-MOF/graphene oxide/ferrocene composite electrode with dual linear ranges (0.01–90 μM and 90–800 μM) and an ultralow detection threshold of 0.003 μM. The platform maintained signal fidelity in the presence of biological interferences and achieved recoveries of 98–103 %, demonstrating excellent selectivity and reproducibility [23].

Expanding further, Wu et al. introduced an electrochemiluminescence (ECL) aptamer sensor using MOF scaffolds to target α-synuclein oligomers, an early biomarker of PD. The device achieved femtomolar detection sensitivity and successfully identified targets in diluted human serum, illustrating the potential of MOFs for next-generation clinical diagnostics (Fig. 3) [24].

Collectively, these investigations underscore the transformative role of MOF-based composites in advancing electrochemical biosensing for PD. By integrating analyte pre-concentration, catalytic functionality, and tailored signal transduction within a single modular framework, these systems achieve sensitivities and selectivities that were previously unattainable. The scope of applications has expanded well beyond dopamine detection to encompass multiplex neurotransmitter analysis, oxidative stress biomarkers such as glutathione, and pathogenic proteins including α-synuclein, while progress in non-invasive and wearable platforms is opening avenues for real-time patient monitoring. Yet, key challenges persist, particularly regarding structural stability under physiological conditions, long-term biocompatibility, and reproducibility of device fabrication. Addressing these issues will require the design of highly conductive and biocompatible MOF composites, integration with closed-loop therapeutic feedback systems, and establishment of standardized performance benchmarks. Looking forward, the convergence of MOF-based sensing technologies with digital health and precision medicine frameworks has the potential to shift PD management from episodic clinical assessments to continuous, personalized monitoring, ultimately enabling earlier intervention and optimized therapeutic outcomes.

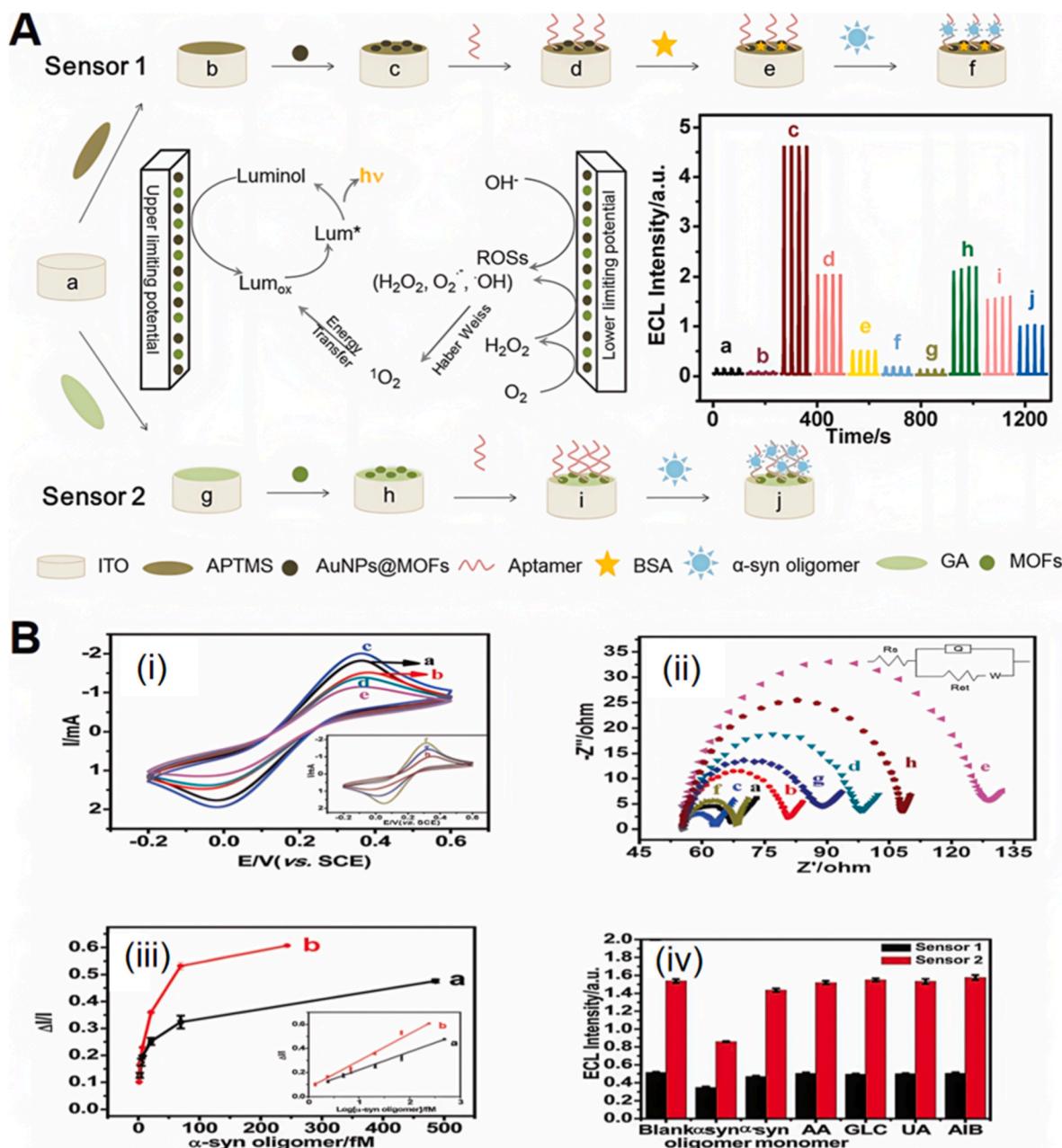


Fig. 3. (A) Schematic illustration of the construction steps and recognition pathway of the designed aptasensors. The inset presents ECL images recorded for: (a) bare ITO, (b) APTMS-modified ITO, (c) AuNPs@Cu-MOFs/ITO, (d) aptamer/AuNPs@MOFs/ITO, (e) sensor 1, (f) sensor 1 following α-syn oligomer binding, (g) GA/ITO, (h) Cu-MOFs/ITO, (i) sensor 2, and (j) sensor 2 after α-syn oligomer interaction. (B) Comparative electrochemical profiles: CV curves at 50 mV s⁻¹ scan rate (i) and EIS spectra (ii) corresponding to (a) ITO, (b) APTMS/ITO, (c) AuNPs@Cu-MOFs/ITO, (d) sensor 1, (e) sensor 1 after α-syn oligomer capture, (f) Cu-MOFs/ITO, (g) sensor 2, and (h) sensor 2 following α-syn oligomer capture. (iii) Correlation between ECL response intensity and α-syn oligomer concentration for sensor 1 (curve a) and sensor 2 (curve b). (iv) Selectivity evaluation showing the influence of possible interfering species on aptasensor performance [24].

Overall, the current investigations indicate that biosafety evaluation remains incomplete and fragmented. Available data on in vivo degradation are restricted to short study periods without robust information on long-term degradation kinetics, coordinated stimulus dependent breakdown, or identification of degradation intermediates under physiological conditions. The covalent frameworks of COFs also raise unresolved concerns regarding partial decomposition and slow tissue accumulation. Further, metabolic fate has not been clarified, including circulation and excretion of metal ions, enzymatic processing of organic linkers, and coupled metabolism in hybrid materials. Immunogenicity has received little systematic attention, with no detailed study of early innate immune activation driven by surface chemistry, delayed adaptive

responses during prolonged administration, or variability in immune risk among sensitive patient groups. Long term toxicity data remain sparse, and current protocols usually employ short exposure intervals, limited toxicity endpoints, and non clinical models that do not reflect conditions relevant to chronic treatment. Addressing these knowledge gaps is essential for reliable clinical translation and regulatory approval of MOFs and COFs.

2.1.2. Fluorescence detection

Although MOF-based electrochemical sensors have already proven effective in quantifying PD biomarkers with high sensitivity, their outputs remain largely limited to bulk concentration measurements. Such

approaches rarely provide insight into the *in situ* distribution or dynamic fluctuations of analytes in cells or tissues. For a deeper understanding of PD pathogenesis, it is essential to visualize biomarker activity in real time and at the microscale. Fluorescence detection, by virtue of its excellent sensitivity, high spatial resolution, and strong imaging capabilities, offers such a complementary strategy. With their tunable structures, large surface areas, and rich pore environments, MOFs have become particularly attractive as scaffolds for constructing fluorescent probes for PD-related diagnostics.

One early demonstration of this potential was reported by Tan and co-workers, who created a carbon dot–MnO₂ inner filter effect probe for label-free and rapid dopamine (DA) detection. The platform enabled analysis within 3 min, with a working range of 1–30 μM, a detection limit of 100 nM, and recovery rates between 102 and 110 %, making it highly suitable for pharmaceutical quality control [25]. While the approach offered low cost and fast operation, its reliance on redox processes made it prone to interference from antioxidants such as ascorbic acid, limiting its use in complex biological matrices. To address these shortcomings, Moghzi et al. developed ultrathin europium-based MOF nanosheets (ECP) as a “turn-on” fluorescent probe. This design

exploited dopamine adsorption on the nanosheet surface and the antenna effect of DA on Eu³⁺ luminescence, producing strong fluorescence enhancement. The system achieved an LOD of 21 nM, recovery rates of 90–99 % in serum, and exhibited high anti-interference capacity against common metabolites along with good stability and reusability [26]. Such results underline the value of rational MOF design in overcoming the selectivity and stability issues often encountered in simpler probe systems.

Building further on dopamine analysis, Xie et al. synthesized Eu-α-cyclodextrin MOF nanoparticles capable of host–guest interactions with DA, achieving a wide dynamic range (10⁻⁹–10⁻⁴ M) and an ultralow detection limit of 0.65 nM [116]. In parallel, Pan and colleagues proposed a ZGC/ZIF-8-NH₂ composite probe based on a photoinduced electron transfer mechanism, which exhibited a detection limit of 75 nM. By incorporating the probe into a chitosan hydrogel patch, they developed a wearable platform for sweat analysis. Combined with smartphone RGB analysis, the device enabled real-time, semi-quantitative, and non-invasive monitoring of DA, illustrating the transition of MOF fluorescence probes from laboratory systems to practical patient-centered applications (Fig. 4) [27].

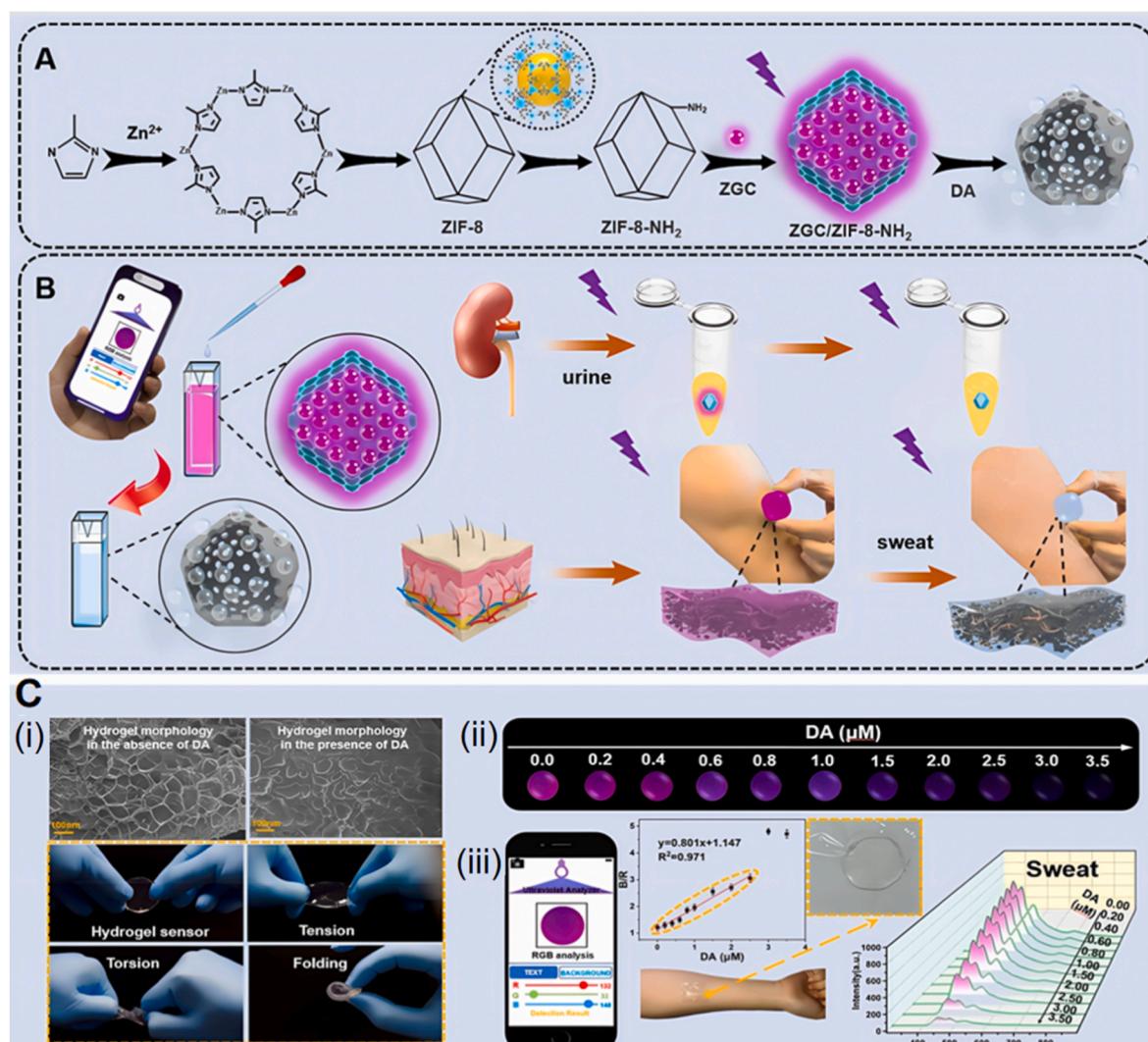


Fig. 4. (A) Fabrication process of ZGC/ZIF-8-NH₂ mesoporous dodecahedron illustrating its colorimetric transition. (B) Conceptual framework of the dual-mode platform: a urine-responsive probe (left) and a hydrogel-based sweat sensor applied as a skin patch (right). (C)(i) Representative SEM image showing hydrogel morphology without dopamine (DA) and following DA exposure; mechanical robustness of the patch under stretching, twisting, and folding conditions. (ii) Photographs of hydrogel color variation with increasing DA concentration under 254 nm UV illumination. (iii) Workflow schematic for DA recognition via smartphone color analysis and visualization of hydrogel patch placement on human skin. Calibration curve correlating R/B ratio with DA concentration. Fluorescence spectra of the hydrogel sensor recorded at different DA levels [27].

Beyond neurotransmitter detection, MOF-based fluorescent probes have also been applied to pathological proteins. A notable example was reported by Miao et al., who created a Tb-MOF@Pt-aptamer probe for α -synuclein (α -Syn). Upon encountering α -Syn in the intestine, the probe exhibited an “on” fluorescence signal, enabling non-invasive diagnosis through fecal analysis with a detection limit of 0.04 pg/mL [28]. This approach demonstrated how MOF-based systems can be extended into in vivo biosensing formats, marking progress toward clinically relevant applications. Expanding the scope further, Chen and colleagues constructed a DNA@MOF hybrid probe (P-DNA@1) for sequential detection of Hg^{2+} and biothiols (Cys, GSH, Hcy) using an “on-off-on” fluorescence mechanism. The sensor achieved nanomolar sensitivity (Hg^{2+} : 3.0 nM; biothiols: 8–15 nM) with high selectivity and stability [29]. In another study, Gong et al. developed a water-stable europium MOF that detected tryptophan and Cu^{2+} through competition for excitation energy, leading to quenching of Eu^{3+} luminescence. The probe achieved detection limits of 0.22 μ M and 0.09 μ M, respectively, and maintained excellent performance in serum samples [30]. Together, these results demonstrate the adaptability of MOFs in multi-analyte detection under complex biological conditions.

Further innovations have combined MOFs with visualization strategies. Wu and co-workers reported a tricolor molecularly imprinted fluorescent sensor (Tri-FMIPs) using NH₂-MIL-88 and CdTe quantum dots for homovanillic acid (HVA) detection. The MOF served as a stable blue reference while quantum dot emission was quenched by HVA, producing a visible color shift from orange to blue. The probe displayed high sensitivity (LOD: 15 nM), a response time of 2 min, and compatibility with smartphone-based quantification, enabling fast, on-site analysis in serum and urine [31]. Similarly, Mir et al. designed an aluminum-based MOF sensor that could rapidly detect both entacapone (an anti-PD drug) and fipronil (a pesticide), with detection limits of 7.6 nM and 2.3 nM, respectively, and strong resistance to interference. This dual-purpose system exemplifies the ability of MOF-based probes to bridge biomedical and environmental monitoring needs [32].

Taken together, these advances clearly demonstrate the versatility of MOF-based fluorescence probes in addressing the multifaceted diagnostic challenges of PD. By integrating molecular recognition, optical amplification, and structural tunability, these systems not only deliver ultrahigh sensitivity but also allow real-time visualization of neurotransmitters, proteins, and metabolites. Their applications have expanded from simple dopamine assays to complex targets such as α -synuclein, homovanillic acid, and even therapeutic drugs, showing their adaptability across diverse contexts. Yet, for clinical translation, key challenges remain: intrinsic tissue autofluorescence, scattering effects, long-term probe stability, and incomplete understanding of MOF metabolism in vivo. Addressing these issues will require designing biocompatible, metabolically traceable MOFs, developing ratiometric or activatable probes to minimize background interference, and ensuring robust validation in physiologically relevant models. Looking ahead, coupling MOF-based fluorescent platforms with wearable devices, smartphone technologies, and multimodal imaging holds great promise for shifting PD diagnostics from static laboratory tests to dynamic, patient-centered monitoring systems, thereby opening new possibilities for early intervention and mechanistic research.

2.1.3. Colorimetry and multi-mode sensors

In addition to electrochemical and fluorescence strategies, colorimetric sensing based on MOFs has emerged as an attractive option for PD diagnostics. These platforms mimic peroxidase-like catalytic reactions to produce visible color changes, offering clear advantages such as simplicity, low cost, and the absence of sophisticated instrumentation. Such features make them highly suitable for rapid, point-of-care testing. More recently, the field has progressed from single-signal readouts toward multi-mode sensing, where complementary detection pathways provide cross-validation, thereby improving sensitivity, selectivity, and clinical reliability. One demonstration of this approach

was reported by Panneerselvam and co-workers, who designed Cu-HMT and Ni-HMT coordination frameworks with intrinsic peroxidase-like activity for dopamine (DA) sensing. By catalyzing the oxidation of chromogenic substrates, these MOF nanoenzymes achieved selective DA detection with a limit of 4.2 μ M. Importantly, their application to human urine yielded recovery values between 93 and 97 %, confirming both robustness and translational relevance. This work provided a foundation for developing simple, non-invasive assays for PD biomarker analysis using MOF-based nanoenzymes [33]. Subsequent advances introduced more sophisticated sensing mechanisms. Abbasi-Moayed et al. developed an “anti-etching” assay in which MIL-88A(Fe) catalyzed the oxidation of TMB to TMB²⁺, which etched gold nanorods (AuNRs), causing a spectral blue shift and a visible color change. The presence of Levodopa inhibited this process, preserving the original color of the solution. By correlating these optical variations with analyte concentration, the system enabled quantitative Levodopa detection [34]. This strategy combined MOF catalysis with plasmonic nanomaterials, producing distinct and label-free colorimetric readouts while highlighting a versatile route for monitoring therapeutic agents.

While single-signal probes are straightforward, their susceptibility to environmental interference can compromise accuracy. To address this, Chen and colleagues constructed a dual-mode platform coupling colorimetric and photothermal outputs using iodide-modified covalent triazine frameworks (Zn-CTF/I). The probe exhibited exceptional sensitivity toward acetylcholinesterase (AChE), with an LOD of 0.003 U L⁻¹, and performed reliably in serum samples [35]. Mechanistic studies revealed that halogen–metal co-regulation of the catalytic center played a critical role in enhancing activity, offering useful insights for the rational design of nanoenzyme catalysts. By combining two orthogonal detection modes, this system significantly improved diagnostic confidence, underscoring the value of multi-signal platforms in PD research. Progress toward clinically relevant targets has also been made in protein biomarker detection. Xu et al. prepared a Cu-MOF@Ag composite decorated with silver nanoparticles to establish a dual-mode immuno-sensor for nitro- α -synuclein. In this system, electrochemical detection provided nanogram-level sensitivity (LOD 0.23 ng/mL), while the colorimetric channel supplied rapid visual confirmation. Application to human serum successfully distinguished PD patients from healthy controls ($p < 0.005$), illustrating the strong diagnostic potential of MOF-based multi-mode platforms for real-world clinical use [36].

Conclusively, colorimetric and multi-mode MOF sensors have evolved from simple enzyme-mimicking assays into versatile analytical systems capable of delivering high sensitivity, visual accessibility, and robust validation. By integrating catalytic activity with orthogonal transduction mechanisms such as plasmonics, photothermal effects, or electrochemical signals, these sensors reduce subjectivity and improve resilience against interference. Despite these advances, challenges remain in ensuring quantitative accuracy, long-term probe stability, and standardization across different assay formats. Future directions should emphasize the development of biocompatible, surface-engineered MOFs with stable catalytic sites, as well as the integration of multi-signal readouts with portable and wearable devices. Coupled with artificial intelligence-driven data interpretation, such systems could shift PD diagnostics from episodic testing to continuous, personalized monitoring, offering powerful tools for both early detection and therapeutic optimization.

2.2. Application of MOFs in PD treatment

The standard pharmacological management of PD continues to rely on dopamine replacement strategies, particularly levodopa therapy. These regimens remain effective in alleviating motor symptoms such as tremor and rigidity, yet they do not alter the underlying neurodegenerative processes [11]. The inability of current treatments to slow or reverse disease progression is linked to the multifactorial nature of PD pathology. Aberrant metal ion homeostasis, protein misfolding and

aggregation, mitochondrial dysfunction, oxidative stress, and chronic neuroinflammation interact in a complex network of damaging events that ultimately drive neuronal loss [36]. Addressing these challenges requires therapeutic platforms capable of modulating multiple pathological pathways simultaneously while ensuring biocompatibility and controlled activity.

A dominant challenge for therapeutic intervention in the central nervous system lies in traversing the blood brain barrier. This highly selective structure restricts entry of most molecular agents and ionic species into brain parenchyma, which significantly limits the effectiveness of nano based strategies in PD management [132]. MOFs provide a strategic advantage for BBB transport because their external surfaces can be engineered with targeting ligands that recognize and bind to specific receptor sites on endothelial cells. This receptor mediated uptake promotes controlled translocation across the barrier and facilitates delivery of therapeutic payloads directly to neural tissue [127 and 128].

MOFs, with their structural tunability, chemical diversity, and ability to integrate multiple functionalities within a single framework, are increasingly being investigated for such purposes [37,38]. Their ordered porosity allows the controlled release of therapeutic ions or molecules, their organic–inorganic hybrid nature provides opportunities for functionalization, and their intrinsic catalytic or enzyme-mimetic properties can be harnessed to regulate cellular microenvironments. Current investigations mainly focus on restoring the homeostasis of metal ions, synergistic regulation of neuroinflammation and related cell death pathways.

2.2.1. Restoring the homeostasis of metal ions

The substantia nigra pars compacta in PD patients shows marked disruption of trace metal metabolism, particularly copper and zinc. These alterations are closely linked to dopaminergic neuronal death, mitochondrial dysfunction, and the aggregation of α -synuclein into Lewy bodies [39]. Conventional supplementation strategies, such as oral copper salts, are limited by low bioavailability, rapid systemic clearance, poor targeting efficiency, and the risk of systemic toxicity including hepatic overload [40]. MOFs provide an attractive solution by combining structural stability with controlled degradation, allowing precise delivery of bioactive ions to target tissues.

Aguila-Rosas and colleagues examined MOF-74(Cu) as a therapeutic copper delivery system. In vitro degradation studies demonstrated a controlled release profile following near zero-order kinetics, with only 30 percent of Cu^{2+} released within 6 h under gastrointestinal conditions, thereby avoiding the sudden burst release commonly observed with conventional copper salts. In vivo biodistribution experiments further confirmed that, compared with copper gluconate, MOF-74(Cu) resulted in lower hepatic accumulation while simultaneously enhancing copper concentrations in brain regions most affected by PD, including the striatum and substantia nigra [41]. This dual benefit of minimizing peripheral toxicity while improving cerebral delivery underscores the promise of MOF-74(Cu) not only for PD but also for other neurodegenerative disorders linked to trace metal deficiencies, such as amyotrophic lateral sclerosis and Menkes disease.

An innovative perspective on ion-based therapy was introduced by Meng et al., who synthesized Archimedean heteroduplex $\text{Ti}_{10}\text{Cd}_6$ nanoclusters and evaluated their therapeutic effects in a PD worm model. The study revealed striking stereochemical dependence: the R-enantiomer rescued dopaminergic neurons, alleviated motor dysfunction, and significantly suppressed α -synuclein aggregation, while the S-enantiomer produced negligible effects [42]. This discovery suggests that biological systems can discriminate between stereoisomers of nanoclusters, leading to fundamentally different outcomes in disease modulation. The work highlights chirality as a previously underappreciated parameter in the design of metal-based therapeutics, offering a new direction for precision medicine in PD. By moving beyond simple supplementation toward stereochemically defined interventions, MOF-derived nanostructures could be tailored for specific disease

pathways with high selectivity.

2.2.2. Integration and regulation of neuroinflammation and cell death pathways

In addition to disruptions in metal ion balance, chronic neuroinflammation is now recognized as a major pathological driver of PD. Microglial overactivation leads to excessive production of pro-inflammatory mediators, while persistent activation of the NLRP3 inflammasome amplifies neurotoxicity. When coupled with elevated reactive oxygen species (ROS), this inflammatory environment exacerbates dopaminergic neuron degeneration [43]. Strategies capable of simultaneously reducing oxidative stress and suppressing inflammasome activity are therefore highly desirable.

MOFs are uniquely suited for this purpose due to their ability to mimic enzymatic activities. Depending on their composition, MOFs can exhibit catalase-like activity to decompose hydrogen peroxide into oxygen and water, or superoxide dismutase-like activity to convert superoxide radicals into less harmful species [44]. These properties allow MOFs to act as multifunctional “nanoenzymes” capable of restoring redox balance while interrupting inflammatory signaling cascades.

Li and colleagues advanced this concept by developing a porphyrinic Zr–Fe MOF encapsulated within mannitol-modified liposomes (Zr–FeP MOF@mannitol). The framework, built from Fe-TCPP ligands coordinated with Zr_6 clusters, displayed dual enzyme-mimicking functions, efficiently scavenging intracellular ROS. Encapsulation in mannitol-functionalized liposomes improved blood–brain barrier permeability and enabled selective accumulation in lesioned brain regions in PD mouse models. In vitro studies revealed that the nanoenzyme system inhibited NLRP3 inflammasome activation by reducing ROS levels, thereby suppressing the production of IL-1 β and IL-6 (Fig. 5) [45]. This multifunctional therapeutic not only reduced inflammatory signaling but also provided neuroprotection, illustrating the potential of MOF-based nanoenzymes to act at the intersection of oxidative stress regulation and immune modulation.

The use of biomimetic enzyme mimics has opened new directions for the construction of MOF based nanozymes. Drawing inspiration from the active site of natural Cu/Zn containing superoxide dismutase, Fan and co-workers developed a Cu-ZIF nanozyme by integrating copper ions into a ZIF-8 framework through a biominerilization route. To increase tissue retention and improve bioavailability, this nanozyme was embedded within a PLGA-PEG-PLGA thermosensitive hydrogel to produce a Cu-ZIF hydrogel composite. The resulting platform exhibited strong superoxide dismutase like catalytic activity, efficiently scavenged superoxide radicals, and produced marked improvement in behavioural and pathological features in PD models. Incorporation of a temperature responsive hydrogel improved local adhesion and extended residence time at the pathological site, leading to enhanced therapeutic performance [46]. This strategy shows that combining MOF derived nanozymes with smart biomaterials can overcome delivery limitations and improve targeted treatment outcomes.

Furthermore, chiral configuration plays a decisive role in the biological performance of nanomedicines. Jiang et al. developed two chiral nanoenzyme systems, Ptzyme@L-ZIF and Ptzyme@D-ZIF, by incorporating platinum catalytic domains within L- and D-type chiral ZIF shells. Comparative evaluation showed that Ptzyme@D-ZIF possessed greater blood–brain barrier penetration and higher brain tissue accumulation than its L-configured counterpart. Mechanistic investigations indicated that the D-type chiral surface promoted transcytosis across the blood–brain barrier through multiple routes, including clathrin-mediated and caveolin-mediated endocytosis, while also exhibiting extended plasma retention. Additional studies revealed that Ptzyme@D-ZIF produced neuroprotective effects by suppressing neuroinflammation-driven apoptosis and ferroptosis (Fig. 6) [47]. These findings highlight chirality as a powerful design variable in nanomedicine, capable of directing biological recognition, transport, and therapeutic response in PD treatment.

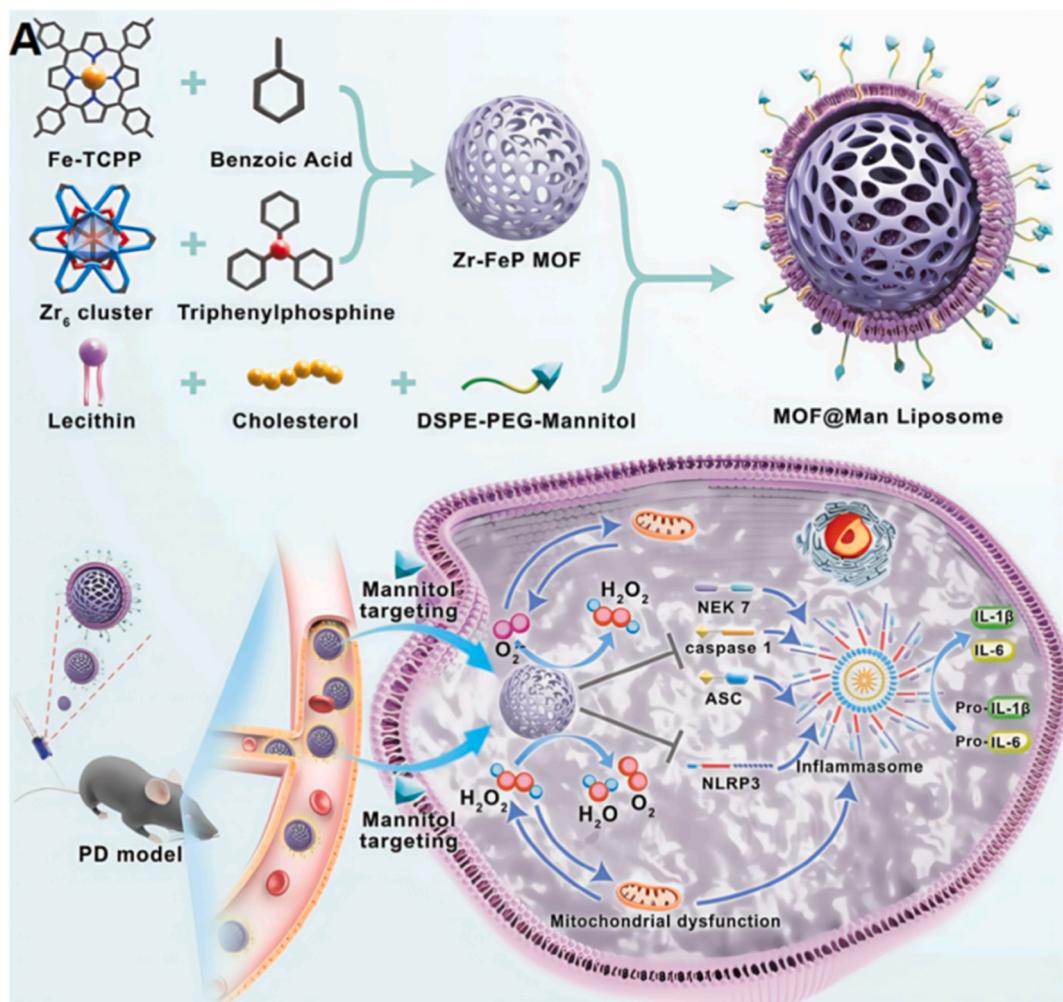


Fig. 5. (A) Representation of the fabrication of the MOF@Man-liposome nanozyme platform and its therapeutic action in PD, achieved by mitigating oxidative stress and neuroinflammation through suppression of NLRP3 inflammasome activation and reduction of pro-inflammatory cytokine release [45].

Together, these examples demonstrate that MOFs can be engineered as active participants in therapy, not merely as passive carriers. By tailoring degradation profiles, incorporating stereochemical control, and exploiting enzyme-mimetic properties, MOFs enable a new generation of therapies capable of addressing multiple dimensions of PD pathology. Continued progress in this field will depend on resolving challenges such as long-term biocompatibility, reproducibility of synthesis, and mechanistic understanding of MOF interactions within neural tissue. If these hurdles are addressed, MOF-based therapeutics hold the promise of moving PD management beyond symptomatic relief toward genuine disease modification.

It is important to highlight that, despite being constructed through distinct design principles, the three reported MOF-based nanoenzyme systems converge in demonstrating potent antioxidant and anti-inflammatory properties. The formulation described by Li and colleagues exerted its effects primarily through catalase- and superoxide dismutase-like activities that efficiently reduced ROS burden [45]. Fan and co-workers pursued a biomimetic strategy by emulating the catalytic features of native SOD, while Jiang's group introduced a stereochemically tuned system that integrated both SOD- and CAT-like functionalities [46,47]. Strategies to improve brain delivery were also distinct yet complementary: mannitol modification facilitated blood–brain barrier transport, structural chirality optimized transcytosis and cerebral accumulation, and the incorporation of a thermosensitive hydrogel enhanced local retention at the lesion site [45–47].

Recently, a chiral gold nanoparticle-ZIF-8 complex (Au-ZIF) was

developed by Chen et al., and efficient blood–brain barrier penetration and brain targeting were achieved through formation of an apolipoprotein-rich protein corona on the D enantiomer. It was demonstrated that D-Au-ZIF regulated the CX3CL1/CX3CR1 chemokine axis between neurons and microglia, inhibited downstream NF-κB signaling, and reprogrammed microglial mitochondrial metabolism by shifting from a pro-inflammatory glycolytic state to an anti-inflammatory oxidative phosphorylation mode. The work proposed that MOF-based nanomedicine could influence coordinated interactions among neurons, microglia, and neural stem cells, establishing a shift from single-target intervention toward systemic modulation of PD related pathological networks [126].

In addition to precise chemical design, the use of external physical stimuli to rapidly and reversibly modulate blood–brain barrier permeability represents a promising intelligent delivery strategy. A nanocomposite material (ZIF-8@PB-QCT) was constructed by Liu et al., in which prussian blue was encapsulated and the natural antioxidant quercetin was loaded. Prussian blue, the central component of this platform, possessed strong photothermal conversion capability. Under near infrared laser irradiation, the localized mild thermal effect reversibly increased blood–brain barrier permeability and induced structural changes in the ZIF-8 shell to achieve on demand quercetin release at the lesion site. This strategy was shown to enhance mitochondrial function in PD models, evidenced by higher ATP levels, reduced oxidative stress, and restoration of dopaminergic neuronal integrity. The underlying mechanism was associated with activation of

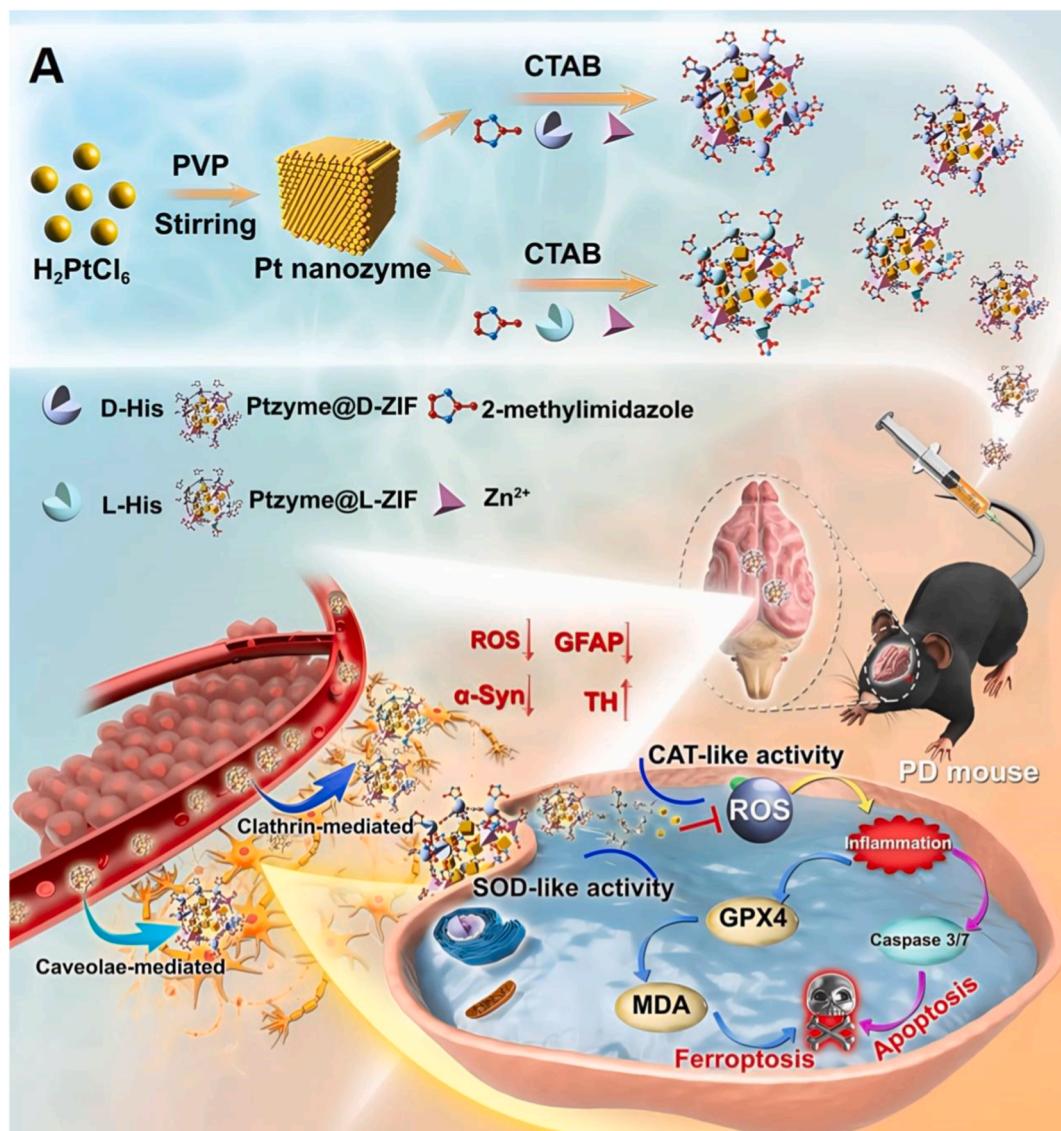


Fig. 6. (A) Conceptual representation of Ptzyme-functionalized L- and D-chiral ZIF frameworks, illustrating their neuroprotective action in PD through simultaneous attenuation of apoptosis and ferroptosis in neurons subjected to oxidative stress and inflammatory imbalance. Abbreviations: PVP, polyvinylpyrrolidone; CTAB, cetyltrimethylammonium bromide; GFAP, glial fibrillary acidic protein; TH, tyrosine hydroxylase; GPX4, glutathione peroxidase 4; MDA, malondialdehyde [47].

the PI3K/Akt signaling pathway [129].

Taken together, these studies demonstrated the versatility of MOFs as therapeutic scaffolds and indicated that the rational integration of catalytic activity, structural chirality, and carrier environment can be combined to enhance neuroprotective outcomes in PD models. Despite this progress, significant challenges still restrict the clinical utility of MOFs for PD treatment. First, long term *in vivo* safety information remains inadequate. Although short-term low toxicity has been reported for systems such as MOF-74(Cu), long-term biocompatibility has been clearly identified as a critical concern. Metal ions including Cu^{2+} and Zr^{4+} may gradually accumulate in tissues such as brain and liver, which presents a risk of chronic toxicity. Second, uncertainties remain regarding degradation related effects. Controlled breakdown of MOFs has only been evaluated over limited time-periods, and long term metabolic pathways and clearance efficiency of both metal ions and organic linkers have not been clarified. These issues may lead to secondary biological damage if not addressed in a systematic manner.

3. Application of COFs in PD

3.1. Smart sensing and monitoring

Covalent Organic Frameworks (COFs) are an emerging family of crystalline porous polymers in which organic building units are interconnected through strong covalent bonds. Unlike conventional porous materials, COFs display highly ordered pore architectures, large surface areas, and structural tunability that can be precisely controlled at the molecular level. Their inherent chemical stability, combined with the possibility of rational functionalization, makes them particularly attractive for biomedical and sensing applications [48–53]. Within the context of electrochemical and optical biosensing, the confined nanochannels of COFs exert spatial effects that influence both the conformation of analytes and their electron-transfer processes. This confinement reduces fouling of the electrode by oxidation by-products, thereby enhancing the reproducibility, selectivity, and durability of the sensor response [3,54,55]. Furthermore, the modularity of COFs enables the deliberate introduction of functional groups capable of engaging in specific host-guest interactions, which is essential for achieving

molecular recognition in complex biological systems.

The relevance of such design features becomes clear when viewed against the clinical backdrop of PD. At present, diagnosis relies predominantly on symptomatic evaluation, which often delays detection to advanced stages and contributes to high rates of misdiagnosis. Reliable biomarker-based assays remain scarce, underscoring the need for materials that can support sensitive and selective detection platforms. Equally important is the therapeutic dimension: although levodopa (*L*-Dopa) remains the cornerstone of PD management, its chronic use does not prevent neurodegeneration and is associated with serious complications. Prolonged therapy leads to motor fluctuations and dyskinesia, which progressively undermine patient quality of life [29,56]. Clinical studies indicate that nearly 75 percent of patients develop such complications within four to six years of treatment, manifesting as “wearing-off” episodes and abrupt “on-off” transitions in motor control [64]. These fluctuations, linked to variable drug bioavailability, highlight the necessity for precise and continuous monitoring of Levodopa concentrations in order to personalize dosage regimens.

Against this backdrop, COFs offer an innovative materials platform for PD diagnosis and therapeutic monitoring. Their ordered porosity and customizable chemistry provide opportunities to construct sensors capable of detecting both disease-related biomarkers and therapeutic agents with high sensitivity and selectivity. In doing so, COFs hold the potential to bridge an existing clinical gap: enabling earlier diagnosis and optimizing drug management, thereby contributing to more individualized and effective treatment strategies for PD.

3.1.1. COF modified electrode for real-time dopamine monitoring

Degeneration of dopaminergic neurons in the substantia nigra results in a marked reduction of dopamine concentration in the striatum, which is one of the most direct biochemical hallmarks of PD. Conventional imaging modalities such as PET and MRI can only provide indirect information on neuronal damage, require long acquisition times, and are often prone to diagnostic uncertainty. By contrast, COF-modified electrodes allow direct quantification of dopamine levels *in vivo*, thereby providing a molecular basis for early diagnosis, disease staging, and therapeutic evaluation [3,57]. Monitoring dopamine dynamics across distinct brain regions such as the striatum and cortex can also reveal pathological disruptions in dopaminergic signaling pathways, deepening our understanding of disease progression [3,58]. The intrinsic confinement effects and charge selectivity of COF nanochannels have been harnessed to design highly selective electrochemical sensors with strong anti-fouling capacity, enabling continuous, real-time analysis of dopamine in animal models of PD [3,59,60].

A notable advance in this direction was reported by Su and colleagues, who fabricated a TpPa-COF-modified carbon fiber microelectrode (cCFE). The COF coating endowed the microelectrode with nanoscale spatial confinement and anti-fouling properties, which significantly improved sensitivity and selectivity for dopamine detection. *In vitro*, the cCFE achieved a detection limit as low as 8.2 nM using differential pulse voltammetry and effectively resisted interference from common electroactive species such as ascorbic acid and uric acid. *In vivo*, implantation of the cCFE into the striatum of living mice enabled real-time monitoring of dopamine release following high-potassium stimulation. Importantly, in PD model mice, the sensor detected striatal dopamine concentrations that were reduced to approximately one half of those in healthy animals, directly reflecting dopaminergic neuronal loss.

The utility of this approach was further highlighted when the cCFE was integrated with levodopa administration to construct a closed-loop therapeutic model. Using this configuration, two low doses of levodopa (0.06 mg g⁻¹ each) maintained dopamine concentrations within the physiological range for more than 50 min, whereas conventional single high-dose administration typically produced transient, excessive dopamine levels. This demonstration of feedback-controlled drug delivery underscores the clinical potential of COF-modified electrodes not only

for neurochemical monitoring but also for guiding personalized treatment regimens. Through systematic *in vitro* testing, physiological simulation, and pathological validation, the TpPa-COF-modified cCFE has established a proof-of-concept platform for real-time, selective dopamine monitoring and dynamic adjustment of therapy in PD (Fig. 7) [3].

3.1.2. COF-based nanomaterials for ultra-sensitive detection of levodopa

The success of COF-modified electrodes in tracking dopamine dynamics illustrates the capacity of these frameworks to combine molecular recognition with high temporal resolution in living systems. However, dopamine itself is not the only analyte critical for PD management. Levodopa (*L*-Dopa), the immediate precursor of dopamine and the most widely prescribed therapeutic, also demands precise monitoring due to its narrow therapeutic index and the high variability of patient responses. Accurate detection of Levodopa is therefore essential not only for assessing treatment efficacy but also for optimizing personalized dosing strategies. Building on the same confinement effects and structural versatility that made real-time dopamine sensing possible, COF-based nanomaterials have been further developed for ultra-sensitive and selective levodopa detection.

Levodopa remains the most effective pharmacological intervention for PD, but its long-term administration is hindered by a restricted therapeutic window and the risk of complications such as motor fluctuations and dyskinesia [62]. As the biochemical precursor of dopamine, Levodopa crosses the blood-brain barrier and is converted into dopamine by monoaminergic neurons, temporarily replenishing striatal dopamine levels. With disease progression, however, the degeneration of dopaminergic neurons and impaired regulation of dopamine storage diminish the therapeutic effect and narrow the dosing margin. Sub-therapeutic doses fail to restore dopamine function, while higher or frequent doses increase the risk of severe side effects, including dyskinesia, cardiovascular disturbances, and vagus nerve-mediated events such as headache, syncope, or cardiac dysfunction [17,63]. Clinical observations indicate that within four to six years of levodopa therapy, up to three-quarters of patients develop dose-related motor fluctuations, highlighting the need for real-time monitoring of drug levels to guide safe and effective treatment.

COFs offer a promising solution to this problem through their ordered pore systems, which can modulate molecular orientation and electrochemical behavior of Levodopa at the electrode interface. The spatial confinement provided by COF nanochannels positions Levodopa molecules perpendicular to the electrode surface, facilitated by hydrogen bonding between the catechol and amino groups of Levodopa and the carbonyl oxygens of the COF skeleton. This orientation decreases the electron-transfer distance and enhances oxidation efficiency. Moreover, the quinoid intermediates generated during *L*-Dopa oxidation are stabilized within the COF pores, preventing polymerization and side reactions, which leads to highly reproducible signals. These interactions amplify electrochemical responses by several orders of magnitude compared with traditional electrodes. An additional advantage arises from the carboxyl group unique to *L*-Dopa, which forms supplementary hydrogen bonds with the COF framework, further improving adsorption stability and signal reliability [60]. This mechanistic synergy explains how COFs can reduce detection limits to the nanomolar range and provide a theoretical foundation for individualized drug monitoring.

A practical demonstration of this approach was presented by Sun and colleagues, who synthesized TAPB-DMTP-COF composites functionalized with silver–cobalt nanoparticles (AgCo/TAPB-DMTP-COF). The COF matrix, prepared from 1,3,5-tris(4-aminophenyl)benzene and 2,5-dimethoxyterephthaldehyde, exhibited a surface area of 2385 m²/g and a pore volume of 1.27 cm³/g, as determined by nitrogen adsorption–desorption analysis. AgCo nanoparticles were uniformly distributed on the COF surface following reduction, as confirmed by high-resolution TEM, while XRD, FTIR, and XPS verified the structural and electronic characteristics of the composite. When applied to glassy

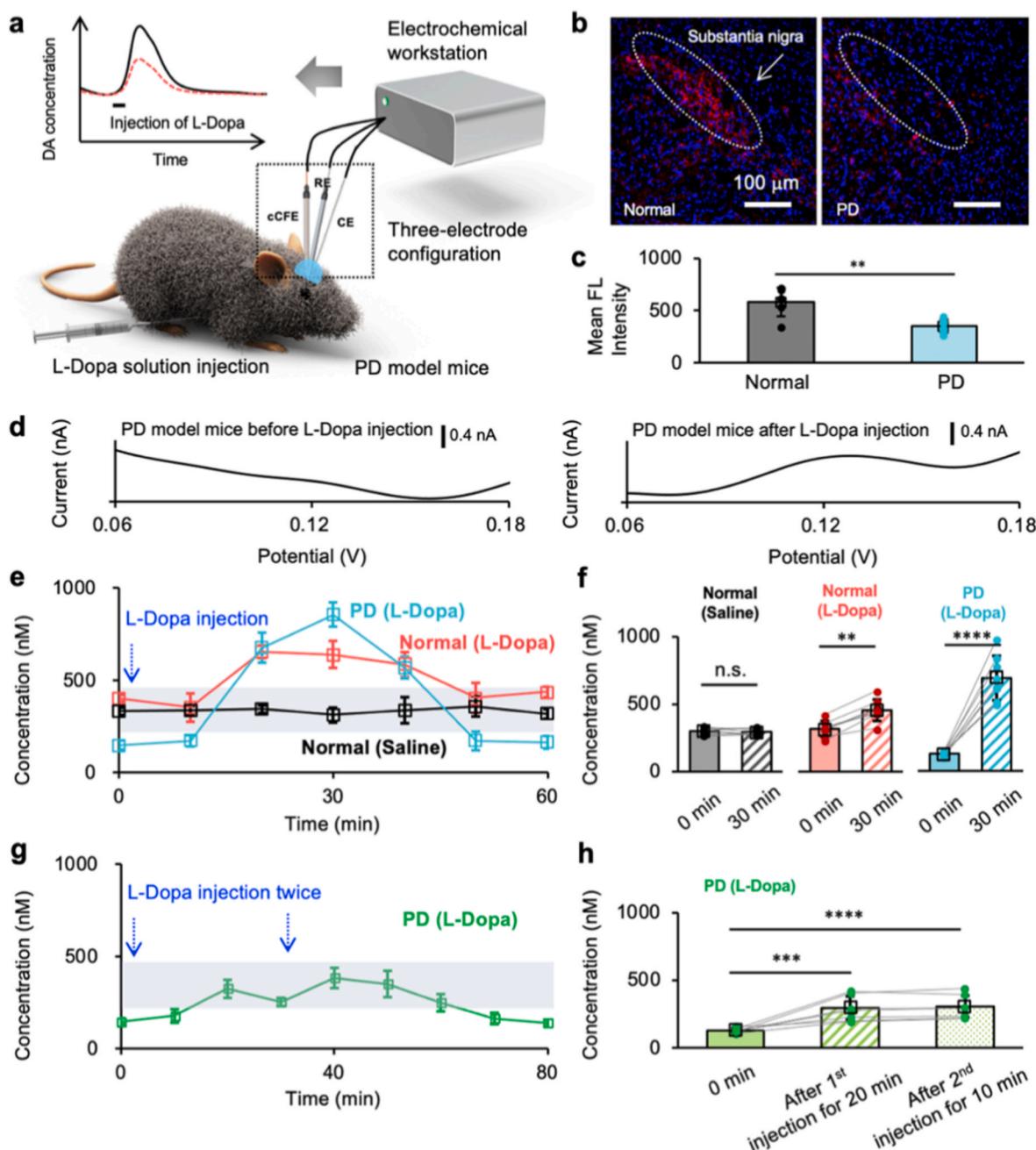


Fig. 7. (a) Feedback-controlled PD diagnosis/therapy using a three-electrode system: cCFE in striatum with Pt counter and Ag/AgCl reference electrodes guided Levodopa dosing. (b, c) Confocal FL images (DAPI, blue; Cy3, red) of normal and PD mouse brains with intensity analysis ($n = 8$). (d–e) DPVs and DA variations in striatum after saline or Levodopa injection (0.13 mg g^{-1}), with physiological DA range indicated. (f–h) Statistical DA levels in normal and PD mice after saline, high-dose, and repeated low-dose Levodopa. Data = mean \pm SD; significance by unpaired Student's t-test ($^*p < 0.05$ to $^{****}p < 0.0001$; n.s.) [3].

carbon electrodes, the composite sensor exhibited a wide linear detection range of $0.01\text{--}100 \mu\text{M}$ and a detection limit of 2 nM ($S/N = 3$). The platform retained 91 % of its catalytic activity after 100 scanning cycles and showed strong tolerance against ionic and carbohydrate interference. Validation in human urine and serum samples yielded recovery rates between 98.0 % and 104.2 %, demonstrating both sensitivity and clinical applicability [65]. This work represents the first example of combining COFs with bimetallic nanoparticles for electrochemical sensing, providing a valuable model for constructing multifunctional sensing platforms.

Taken together, these studies confirm that COF-based materials are capable of detecting levodopa with exceptional sensitivity, stability, and selectivity. They extend the role of COFs beyond dopamine monitoring

to encompass therapeutic drug tracking, offering a pathway toward closed-loop, personalized treatment systems. Despite these advances, challenges remain in ensuring long-term biocompatibility, structural stability under physiological conditions, and reproducibility across different biological matrices. Future research directions should include the design of next-generation COFs with enhanced biostability, the creation of multifunctional COF-nanoparticle composites, and the integration of COF sensors into wearable or implantable devices. Coupling these platforms with artificial intelligence-driven data analysis could accelerate translation from laboratory studies to clinical practice, ultimately enabling real-time, patient-specific management of PD.

3.2. Targeted drug delivery

The blood-brain barrier (BBB) is a highly specialized interface formed by endothelial cells, basement membrane, pericytes, and astrocytic end-feet. This structure maintains central nervous system homeostasis by strictly regulating molecular exchange, blocking toxins and pathogens from entering brain tissue [66]. While protective, the BBB also poses a formidable obstacle for therapy, as most pharmacological agents particularly polar molecules and macromolecular drugs cannot readily cross into the brain parenchyma. This barrier is one of the principal reasons why many compounds with demonstrated efficacy *in vitro* or *in vivo* fail to translate into effective treatments for PD [67]. Covalent modification indirectly influences the adsorption behavior of the blood protein corona by altering the surface physicochemical properties of nano-carriers, thereby changing their *in vivo* circulation time and stability.

COFs have recently emerged as attractive candidates for drug delivery across the BBB owing to their crystalline frameworks, ordered porosity, and high surface area. Their tunable pore size allows efficient encapsulation of drug molecules through noncovalent interactions such as hydrogen bonding and π - π stacking. Furthermore, the modular nature of COFs makes it possible to introduce targeting moieties by synthetic design or post-synthetic modification. For example, surface grafting of peptides such as RVG can promote binding to neuronal receptors and enhance BBB penetration, while modulation of particle size and surface charge enables further control over biodistribution. In addition, COFs can be engineered to release their cargo in response to local stimuli. Acid-sensitive coordination bonds, redox-sensitive linkages, or photothermal triggers under near-infrared irradiation can achieve spatiotemporally controlled release, thereby addressing the common limitations of conventional formulations, including poor loading efficiency, lack of targeting, and uncontrolled drug leakage [68].

3.2.1. COF materials for targeted delivery of levodopa

Levodopa remains the cornerstone of PD therapy because it replenishes dopamine by crossing the BBB and undergoing enzymatic conversion in surviving monoaminergic neurons. However, clinical use is compromised by poor oral bioavailability, rapid peripheral metabolism, and highly variable plasma concentrations. On average, only about one-third of orally administered levodopa reaches systemic circulation, with the remainder undergoing extensive degradation in the gastrointestinal tract and liver. This leads to substantial interpatient variability and frequent peripheral side effects such as nausea, vomiting, and orthostatic hypotension [3,60,61]. Furthermore, levodopa interacts with multiple co-administered drugs, including vitamin B6 and antidepressants, which can compromise efficacy or safety. Over time, the reduced capacity of the brain to buffer dopamine narrows the therapeutic window, making patients increasingly susceptible to motor fluctuations, “wearing-off” effects, and dyskinesia [17,63].

To address these challenges, several delivery systems have been explored, including sustained-release formulations, intestinal infusion, and drug combinations. Yet each strategy carries limitations: sustained-release systems often fail to provide stable plasma levels, and infusion pumps are invasive and difficult to maintain. COF-based nanocarriers present a promising alternative by enabling high drug loading and controlled release through their ordered pore structures. Encapsulation of levodopa within COFs not only protects it from premature peripheral metabolism but also allows release to be triggered by environmental cues such as pH or enzymatic activity. Moreover, combining COFs with external stimuli such as photothermal agents permits precise temporal control over drug release, which is particularly advantageous for neurological disorders requiring fine-tuned dosing. These advances highlight the potential of COFs to overcome bioavailability limitations and improve the therapeutic index of levodopa [69].

3.2.2. COF materials as carriers for BBB penetration

The BBB is often described as a “selective gate” that maintains neural homeostasis by allowing essential nutrients such as glucose and amino acids to enter the brain while excluding most drugs and toxins. Its structural integrity, ensured by tight junctions between endothelial cells and supported by astrocytic and pericytic networks, makes it one of the most difficult biological barriers to penetrate. While this protects the brain from harmful insults, it also severely restricts the treatment of disorders such as PD, Alzheimer’s disease, and glioma [45,57]. In recent years, strategies such as ligand-mediated transport (using transferrin, RVG peptides, or mannitol modification), intranasal administration, and external triggers like near-infrared light have been investigated to facilitate passage of therapeutic agents across the BBB. These approaches demonstrate that carefully engineered nanocarriers can improve drug localization to diseased regions while minimizing exposure of healthy tissue.

Nanotechnology has therefore opened new possibilities for bypassing or modulating the BBB. The small size, high surface area, and chemical versatility of nanomaterials make them suitable for exploiting mechanisms such as receptor-mediated endocytosis, transcellular transport, and even controlled paracellular passage (Fig. 8) [69]. COFs, in particular, stand out due to their modular organic frameworks, ordered porosity, and functional adjustability. These features not only allow efficient encapsulation and protection of therapeutic payloads but also permit precise surface modification for targeted brain delivery. With rational design, COFs can be tailored to cross the BBB through specific recognition pathways, respond to local stimuli within diseased regions, and release drugs in a controlled manner, positioning them as a highly promising class of carriers for central nervous system therapy.

Collectively, recent advances highlight the versatility of COFs as next-generation carriers for brain-targeted drug delivery in PD. Their ordered pore systems and high surface areas enable efficient encapsulation of levodopa and other therapeutic agents, while their chemical tunability allows incorporation of targeting ligands and stimulus-responsive release mechanisms. These attributes directly address the central challenges of PD therapy, including poor bioavailability, peripheral metabolism, and the restrictive nature of the blood-brain barrier. Importantly, the same structural features that allow precise levodopa release can be adapted for the delivery of neuroprotective agents, anti-inflammatory molecules, or gene therapeutics, extending the therapeutic reach of COFs well beyond dopamine replacement. Future directions should emphasize integrating COF carriers with noninvasive delivery routes, optimizing biocompatibility and long-term stability, and developing multifunctional systems capable of simultaneous therapy and real-time monitoring. By bridging the gap between controlled drug transport and targeted brain delivery, COFs hold the potential to redefine precision medicine approaches for PD.

In conclusion, covalent organic frameworks represent a promising new class of porous materials with significant potential in targeted drug delivery for PD. Through rational design and functionalization, COFs can achieve efficient drug encapsulation, targeted transport, and stimulus-responsive release of therapeutics such as levodopa and neuroprotective agents. These properties directly address the limitations of conventional therapies, including poor bioavailability, systemic side effects, and lack of controlled dosing, thereby improving treatment outcomes and reducing complications. Looking forward, advances in materials science, nanotechnology, and biomedical engineering are expected to further expand the capabilities of COFs, enabling the development of multifunctional delivery systems that combine therapy with diagnostic monitoring. With continued progress, COF-based platforms may evolve into integral tools for precision medicine in PD, offering renewed prospects for effective management and better quality of life for patients.

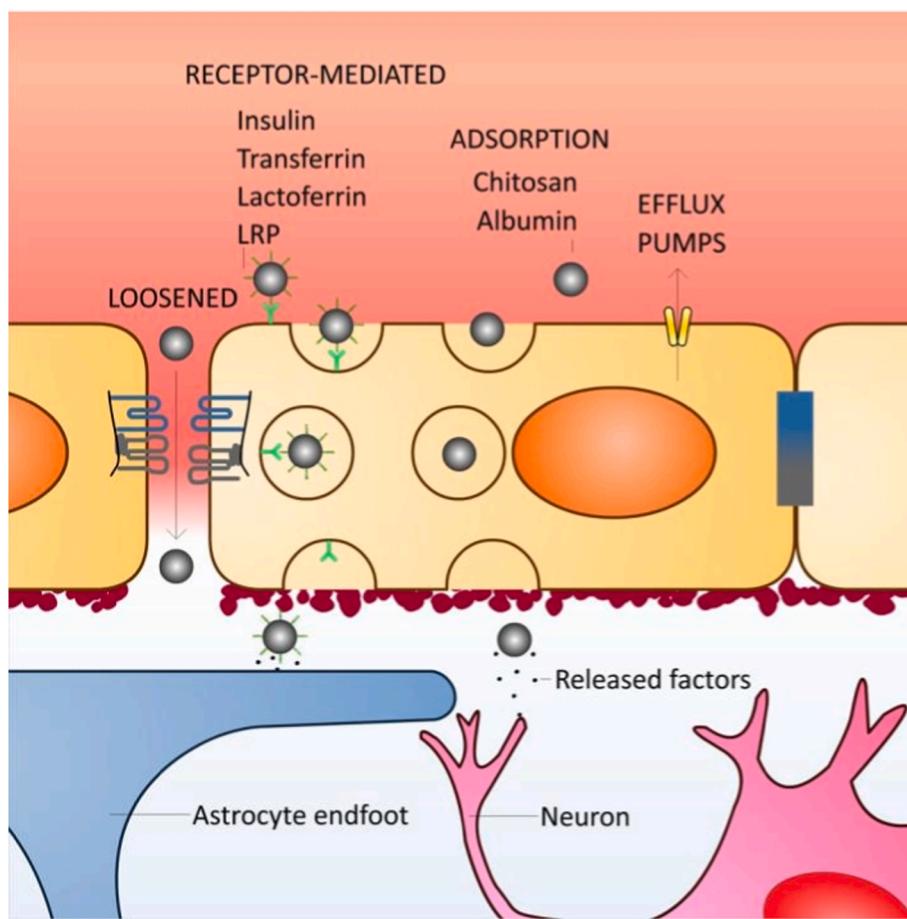


Fig. 8. Transport mechanisms of nanoparticles (NPs) across the blood–brain barrier (BBB). Tight junction disruption allows paracellular passage, while receptor-mediated transcytosis—enabled by ligands or surfactant–apolipoprotein interactions is the primary route. Adsorptive transcytosis also supports brain uptake, whereas efflux pumps reduce NP retention in the parenchyma [69].

3.3. Vector optimization for cell and gene therapy

Conventional treatments for PD, including pharmacological agents, surgical interventions, and rehabilitative approaches, offer symptomatic relief but suffer from inherent limitations. Long-term drug administration is frequently associated with diminishing efficacy and adverse effects, while surgical methods carry procedural risks and are suitable only for selected patients [70]. In recent years, advances in nanotechnology and gene editing have opened new avenues for more durable interventions. Among these, cell and gene therapy is emerging as a particularly promising strategy and has become a central focus in PD research [71].

Within this framework, covalent organic frameworks (COFs) have attracted considerable interest as vectors due to their modular structures and tunable physicochemical properties. COFs are crystalline porous polymers with high surface areas, adjustable pore sizes, structural diversity, and excellent thermal and chemical stability [54]. Their frameworks can be readily functionalized, enabling the attachment of ligands, biomolecules, or targeting groups. These features make COFs attractive candidates for delivering therapeutic genes, proteins, or even engineered cells, as they can combine efficient loading with controlled and site-specific release. In the context of PD, such design flexibility provides a foundation for tailoring interventions to address the complex, multifactorial pathology of the disease [72,73].

3.3.1. COF materials for inhibition of α -synuclein aggregation

α -Synuclein is one of the most critical pathological markers and therapeutic targets in PD. Under physiological conditions, it is a soluble

protein, but pathological misfolding drives the formation of oligomers and fibrils, which eventually accumulate as Lewy bodies. These aggregates exert neurotoxic effects on dopaminergic neurons, leading to progressive motor impairment. Evidence suggests that α -synuclein pathology may originate in the gastrointestinal tract and propagate to the brain via the vagus nerve, lending support to the “intestinal origin” hypothesis of PD. The protein itself is small, comprising 140 amino acids, chiral in nature, and present at extremely low concentrations in body fluids (100–250 pg/mL), which makes reliable detection and therapeutic targeting highly challenging [74].

The structural characteristics of COFs make them well suited to address this problem. Their extended porosity and large surface areas provide abundant binding sites for capturing protein monomers or oligomers, which can hinder further aggregation [74]. By carefully tuning pore size and incorporating functional groups, COFs can achieve selective recognition and inhibition of α -synuclein, effectively stabilizing its non-pathogenic forms [75]. Furthermore, COFs can serve as carriers for small molecules or bioactive compounds with anti-aggregation activity, enabling synergistic therapeutic effects through combined adsorption and drug release (Fig. 9) [76].

Metal ions such as Cu^{2+} and Fe^{3+} are known to accelerate α -synuclein aggregation through redox-mediated pathways, thereby amplifying its toxicity [74]. Functionalized COFs bearing groups such as imines or carboxylates can coordinate with these ions, reducing their availability to promote aggregation. For example, imine-linked COFs have been shown to form stable complexes with Cu^{2+} , significantly attenuating its aggregation-inducing effect on α -synuclein [77]. This dual ability to directly capture protein assemblies and modulate metal

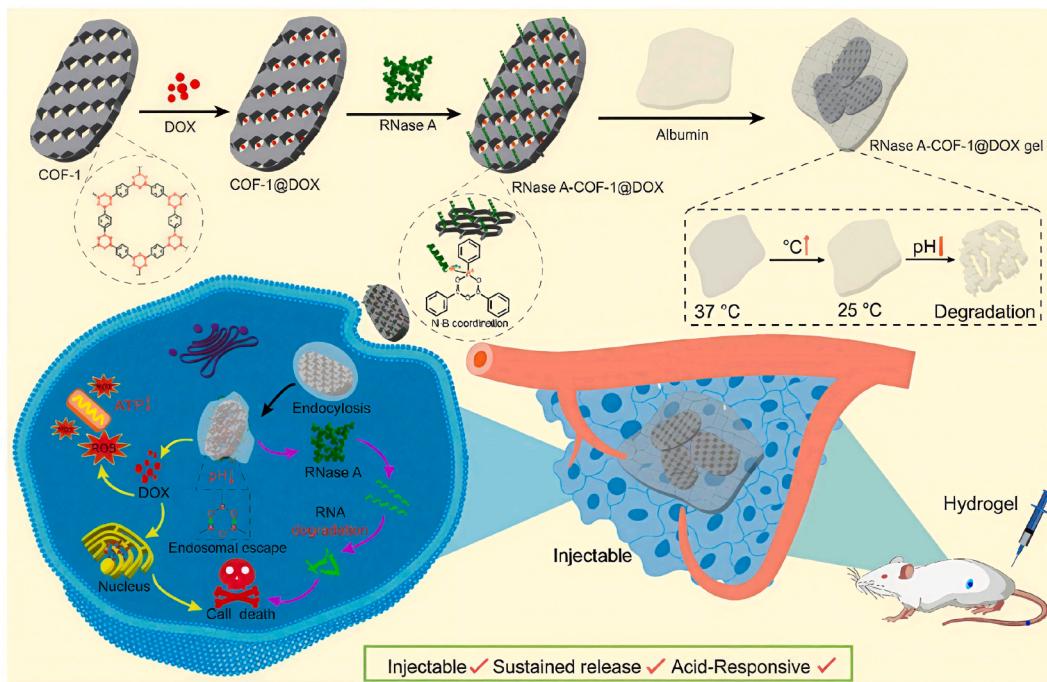


Fig. 9. Diagrammatic representation of the RNase A-COF-1@DOX hydrogel platform and its mode of action for the co-delivery of proteins and low-molecular-weight therapeutics [76].

ion cofactors underscores the promise of COFs as multifunctional agents for preventing pathogenic α -synuclein aggregation in PD.

Conclusively the integration of COFs into cell and gene therapy platforms presents an exciting frontier for PD treatment. Their structural versatility allows them to serve both as delivery vehicles for therapeutic genes and as active modulators of pathological protein aggregation. By combining precise molecular recognition, high drug or biomolecule loading, and tunable release mechanisms, COFs can simultaneously address multiple pathological drivers of PD. Future efforts should focus on enhancing the biocompatibility and long-term stability of COF-based systems, while also exploring multifunctional designs capable of coupling gene delivery with direct neuroprotection. With continued innovation, COFs could become central tools in next-generation therapeutic strategies, bridging molecular targeting with regenerative medicine to provide more durable and disease-modifying interventions for PD.

3.3.2. COF materials as gene therapy vectors

Gene therapy is a therapeutic approach in which functional or corrective genes are introduced into patients to repair or supplement defective ones [78]. In PD, where complex genetic and molecular abnormalities contribute to disease progression, COF-based systems are being explored as promising non-viral gene delivery platforms. Compared with traditional vectors, COFs offer several inherent advantages, including high gene-loading capacity, protection of nucleic acids from enzymatic degradation, controllable release profiles, and the ability to integrate multiple therapeutic modalities within a single platform [79].

The ordered pore structures and large surface areas of COFs provide abundant binding sites for diverse genetic cargos, ranging from plasmid DNA to siRNA and mRNA. A representative study by Li and colleagues exemplifies this potential. They synthesized cationic COFs using a porphyrin-based photosensitizer monomer (TAPP) and a quaternary ammonium salt monomer (Ab) via a solvothermal method, followed by aniline-assisted molecular etching to generate COF nanoparticles (COFNPs) with uniform morphology and an average size of approximately 80 nm. Structural characterization revealed well-defined

porosity (pore diameter 2.38 nm), high specific surface area, and a strongly positive surface charge (zeta potential +36.7 mV), all of which are favorable for electrostatic interaction with nucleic acids.

The gene-loading capacity of these nanoparticles was demonstrated using luciferase siRNA (siRNA-Luc) as a model. Agarose gel electrophoresis confirmed that at a COFNP-to-nucleic acid mass ratio of 40:1, siRNA was completely bound to the carrier, with no residual free nucleic acid detected, indicating efficient loading. Importantly, dynamic light scattering showed that the particle size of COFNPs remained stable after siRNA incorporation, underscoring the structural robustness of the system. To further validate functionality, the researchers loaded siPD-L1 (small interfering RNA targeting PD-L1) onto the COFNPs. Reverse transcription quantitative PCR analysis revealed that COF/siPD-L1 complexes reduced PD-L1 mRNA expression in CT26 cells by approximately 60 %, confirming both delivery efficiency and successful gene silencing [80].

This study highlights how the porosity and surface functionality of COFs can be harnessed for high-capacity nucleic acid delivery while maintaining carrier stability. Beyond siRNA, similar strategies could be adapted for plasmid DNA or mRNA-based therapies, potentially enabling cell reprogramming or neuroprotective protein expression in PD models. Thus, COFs represent a versatile and modular platform for advancing gene therapy approaches in neurodegenerative disease, bridging the gap between nanoscale material design and therapeutic genetic modulation.

In summary, covalent organic frameworks possess a unique combination of high surface area, tunable pore dimensions, structural versatility, biocompatibility, and ease of functionalization, making them attractive candidates for advancing cell- and gene-based therapies in PD. Despite these advantages, their biomedical application remains at an early stage, with only preliminary demonstrations of feasibility in PD models. Key barriers still include ensuring long-term safety and compatibility within the brain microenvironment, achieving efficient penetration of the blood-brain barrier, and developing scalable synthesis methods that maintain reproducibility and quality control. Future progress will depend on rational structural engineering of COFs, the incorporation of targeting ligands or stimuli-responsive functionalities,

and the integration of COF carriers with multimodal treatment strategies. Equally important will be translational efforts aimed at bridging laboratory success with clinical practice, which requires systematic evaluation of pharmacokinetics, immunogenicity, and long-term outcomes. With these developments, COFs could evolve from experimental delivery vehicles into clinically relevant platforms, offering powerful new tools for precision therapy in PD.

4. Artificial intelligence in Parkinson's disease

Artificial intelligence (AI) is increasingly being recognized as a transformative tool in PD research. Its applications range from probing disease mechanisms and identifying pathological signatures, to selecting therapeutic targets and improving the efficiency of clinical trials. Within the scope of this review, particular attention is given to the contribution of AI in early detection, continuous disease monitoring, and adjuvant therapeutic strategies.

4.1. Early symptom detection

4.1.1. Detection of biomarkers

The discovery of reliable biomarkers at the prodromal stage is a cornerstone for timely intervention in PD. Traditional approaches such as magnetic resonance imaging (MRI) and pathological examination provide valuable insights but are constrained by high cost, limited accessibility, and insufficient sensitivity for early disease processes. AI-driven analytical frameworks have begun to address these challenges, offering enhanced accuracy, efficiency, and interpretability.

MRI-based studies represent one of the most active areas of AI application. A representative framework combines three-dimensional MRI with gradient boosting algorithms to achieve high-precision classification of early PD cases. By incorporating explainable AI (XAI) methods, model interpretability is improved, while synthetic minority oversampling (SMOTE) mitigates the imbalance inherent to clinical datasets. Through systematic feature extraction and validation, this strategy demonstrates reliable accuracy in distinguishing PD pathology, highlighting its potential for providing objective biological evidence in early diagnosis [81]. Using chemical exchange saturation transfer magnetic resonance fingerprinting (CEST-MRF), these approaches achieve comprehensive metabolite imaging within 8.25 min, overcoming the temporal and resolution limitations of traditional methods [82].

Efforts have also extended to the integration of imaging with genetic information. An interpretable deep learning model, PIDGN, was designed to combine single nucleotide polymorphism (SNP) data with structural MRI features from the Parkinson's Progression Markers Initiative (PPMI). This multimodal fusion approach compensates for the limitations of single-modality datasets, enabling both precise early prediction of PD and the identification of associations between genetic loci, brain regions, and disease risk [83]. Similarly, Joomee Song and colleagues developed a deep learning-based brain segmentation system that integrates convolutional neural networks (CNNs) with vision transformers (ViTs). Compared with conventional non-AI methods such as FreeSurfer, the model substantially improves segmentation speed and diagnostic accuracy, providing a practical tool for differentiating PD from Parkinson-plus syndromes and supporting large-scale longitudinal studies [84].

AI models have also been directly applied to MRI image classification. For instance, a CNN trained on a Kaggle dataset containing 442 MRI scans (221 PD patients and 221 healthy controls) successfully identified characteristic structural changes associated with PD. Trained and validated on the Google Colaboratory platform, the model exhibited robust recognition accuracy, demonstrating the potential for cost-effective deployment in clinical practice (Fig. 11) [85].

Beyond neuroimaging, AI has been applied to other non-invasive modalities. A deep learning model trained on electrocardiogram (ECG) data was able to predict the risk of developing PD up to five years prior

to symptom onset. Given the widespread use and low cost of ECG, this strategy offers promise for scalable population-level screening and early risk stratification [86]. Another study employed an XGBoost model to analyze aqueous humor proteomic data, enabling estimation of molecular age at both global and cell-type-specific levels (Fig. 10) [87].

Most recently, spectral data have been harnessed for biomarker discovery. A model integrating fully connected neural networks (FNN) with ensemble machine learning (EML) achieved a predictive accuracy of 90.2 % when processing high-dimensional spectral datasets. The method is notable for its efficiency and low cost, offering a scalable approach to biomarker-based early detection [88].

Overall, AI has significantly advanced the landscape of biomarker discovery in PD by improving sensitivity, accelerating analysis, and broadening the scope of measurable signals. From MRI and multimodal genetic integration to ECG, proteomic profiling, and spectral analysis, these approaches collectively demonstrate that AI can overcome many of the limitations of conventional diagnostic tools. Future research should prioritize cross-cohort validation, harmonization of multimodal datasets, and the translation of predictive models into clinically accessible platforms. Such progress will be essential to realize the full potential of AI-enabled biomarker detection for early diagnosis and timely therapeutic intervention in PD.

AI-aided covalent organic frameworks (COFs) hold great promise for PD treatment. AI can optimize COF design by leveraging PD biomarkers identified via multi-modal analytics, enabling precise loading of therapeutic agents and targeted delivery to affected brain regions. Biodegradable COFs with tumor microenvironment-responsive properties can be adapted for PD, achieving controlled drug release while reducing off-target effects. AI further facilitates real-time monitoring of COF degradation, metabolic pathways, and therapeutic efficacy using neuro-imaging or proteomic data, addressing biosafety concerns. This integration advances early intervention and personalized therapy, bridging the gap between diagnostic precision and therapeutic effectiveness in PD.

4.1.2. Early clinical diagnosis

Conventional evaluation of PD motor symptoms relies primarily on clinician-administered rating scales such as the MDS-UPDRS. While widely adopted, these scales are inherently subjective, vulnerable to inter-rater variability, and insufficiently sensitive to subtle fluctuations across treatment cycles. Artificial intelligence (AI)-based digital biomarkers, particularly those extracted from video, handwriting, and speech analysis, are emerging as a means to provide objective and reproducible assessments.

Video-based kinematic analysis has proven particularly effective in quantifying treatment response. A study that examined recordings of 154 PD patients across different levodopa doses employed linear mixed-effects models to link dose-dependent kinematic parameters with age-adjusted outcomes. This approach not only enabled precise monitoring of dopaminergic effects but also suggested a pathway for tailoring individualized dosing strategies [63]. Extending this concept, the AI WALKUP smartphone platform was developed to assess six clinically significant MDS-UPDRS items, including tremor and finger tapping, by extracting motion features such as joint angles and distances. Feature extraction with *tsfresh* allowed conversion of raw movements into structured time-series data, supporting quantitative classification of motor function [89]. In parallel, the MoDAS system, based on the YOLO-X deep learning algorithm, demonstrated remarkable concordance with expert clinicians. With acceptable accuracy exceeding 98 %, MoDAS shows how scalable vision-based models could standardize routine motor assessments [90].

The integration of multimodal datasets offers another path toward robust early diagnosis. By combining features derived from imaging and electronic health records, one recognition framework fused data using Pearson correlation coefficients to eliminate redundancy, followed by machine learning classification [91]. Simpler tasks can also yield

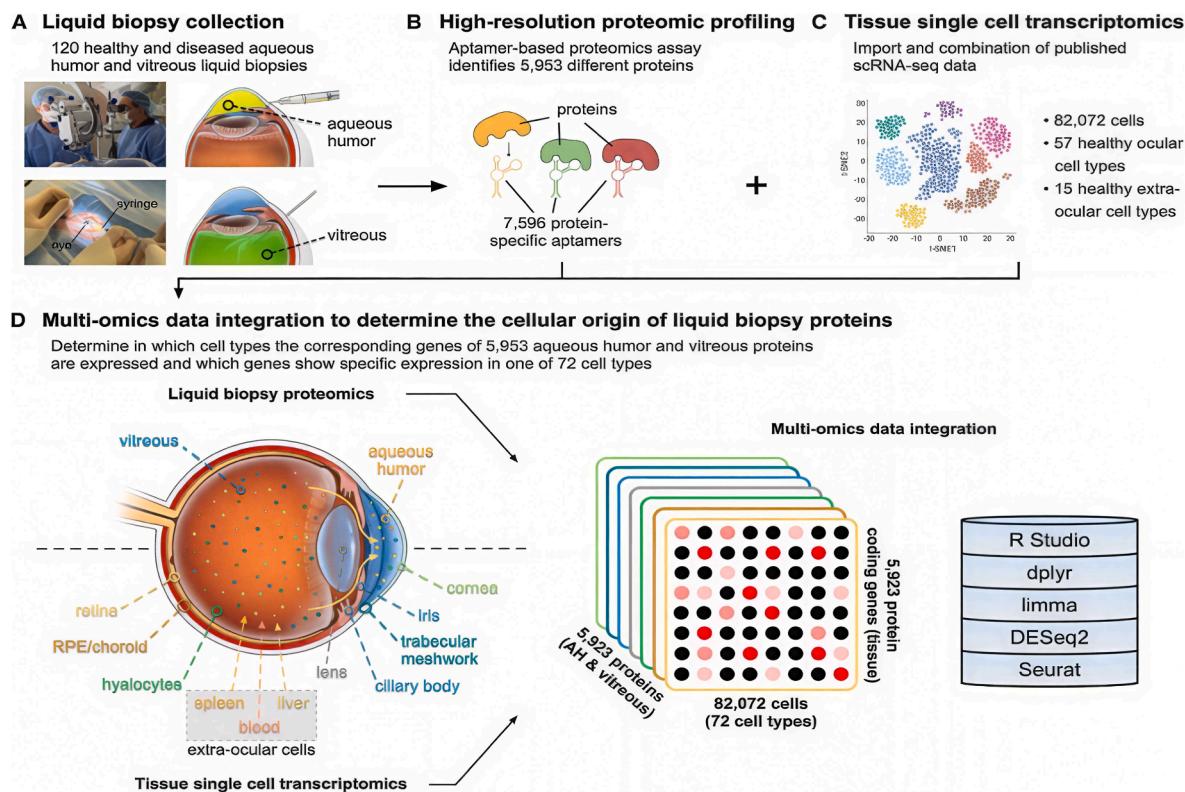


Fig. 10. Schematic illustration of the TEMPO multi-omics workflow for tracing the source of liquid-biopsy proteins. (A) Aqueous humor (AH) and vitreous samples were collected from patients undergoing ocular surgery. (B) Proteomic signatures were characterized through an aptamer-based analytical platform. (C) To identify the cellular expression patterns of genes corresponding to these proteins, single-cell RNA sequencing datasets from normal ocular and periocular cell populations were integrated with the proteomic data. (D) Proteins detected in AH and vitreous samples are visualized as dots localized to the anterior or posterior chambers of the eye, with dot color denoting the cellular origin of each protein. RPE = retinal pigment epithelium [87].

diagnostic value: a binary classifier analyzing Archimedean spirals achieved an accuracy of 95.24 % and has been incorporated into the NeuroPredict platform, demonstrating that accessible, pen-and-paper inputs can serve as reliable diagnostic proxies [92].

Voice analysis has emerged as another rich source of digital biomarkers. A hybrid framework integrating self-organizing maps and neuro-fuzzy systems achieved robust prediction of UPDRS scores from acoustic features, with superior accuracy compared to conventional approaches [93]. Advances in federated learning have further extended this work, enabling models trained on multilingual speech datasets using Wav2Vec 2.0 embeddings to achieve high generalizability while preserving data privacy [94]. Synthetic data generation has also been leveraged: among TVAE, CTGAN, and CopulaGAN, the latter proved most clinically interpretable, enabling reliable diagnostic classification when combined with traditional machine learning [95]. Beyond acoustic biomarkers, handwriting analysis continues to provide valuable indicators. For example, an SVM classifier optimized by PCA achieved 76.25 % accuracy in template drawing tasks, demonstrating utility as a pre-assessment system for rapid clinical screening [96].

Collectively, these approaches illustrate how AI-driven digital biomarkers can overcome the limitations of traditional rating scales. By capturing kinematic, acoustic, and written signatures with high precision, they provide objective tools for early diagnosis and disease staging. Yet, challenges remain: most systems require validation in larger, ethnically diverse cohorts, and standardization across devices is essential to ensure reproducibility. The integration of multimodal biomarkers into unified platforms will be critical to transforming these promising prototypes into clinically deployable tools.

4.2. Application of auxiliary means

4.2.1. Facilitation of medical decision-making

AI is increasingly being incorporated into clinical workflows, not as a replacement for clinicians but as an augmentation tool that provides continuous monitoring, interpretable predictions, and decision support. The Patrika conversational logging system exemplifies this trend, replacing conventional diary-based symptom reporting with an interactive AI interface. Over a two-week deployment, it demonstrated superior reliability by reducing the subjectivity and incomplete reporting associated with self-logging in patients experiencing motor impairments [97].

Beyond symptom diaries, frameworks such as ClinkAIOps have taken integration further by creating closed feedback loops between patients, clinicians, and AI developers. Wearable sensors capture motor fluctuations and drug concentrations in real time, while AI models analyze these data to recommend dose adjustments or identify trends invisible to clinicians. Such systems represent the foundation of precision medicine in PD, where treatment plans evolve dynamically with patient physiology (Fig. 12) [98].

In advanced therapies such as deep brain stimulation (DBS), AI has demonstrated utility in patient stratification. A retrospective analysis of 120 DBS-STN patients applied mRMR feature selection to MRI data, followed by classification using machine learning. The random forest model achieved AUC values close to 1.0, offering reliable prognostic predictions of treatment outcome and informing clinicians in preoperative planning [99].

4.2.2. Therapeutic assistance

AI-assisted rehabilitation is another rapidly expanding frontier. The AiCareGaitRehabilitation system integrates multimodal sensors with IoT

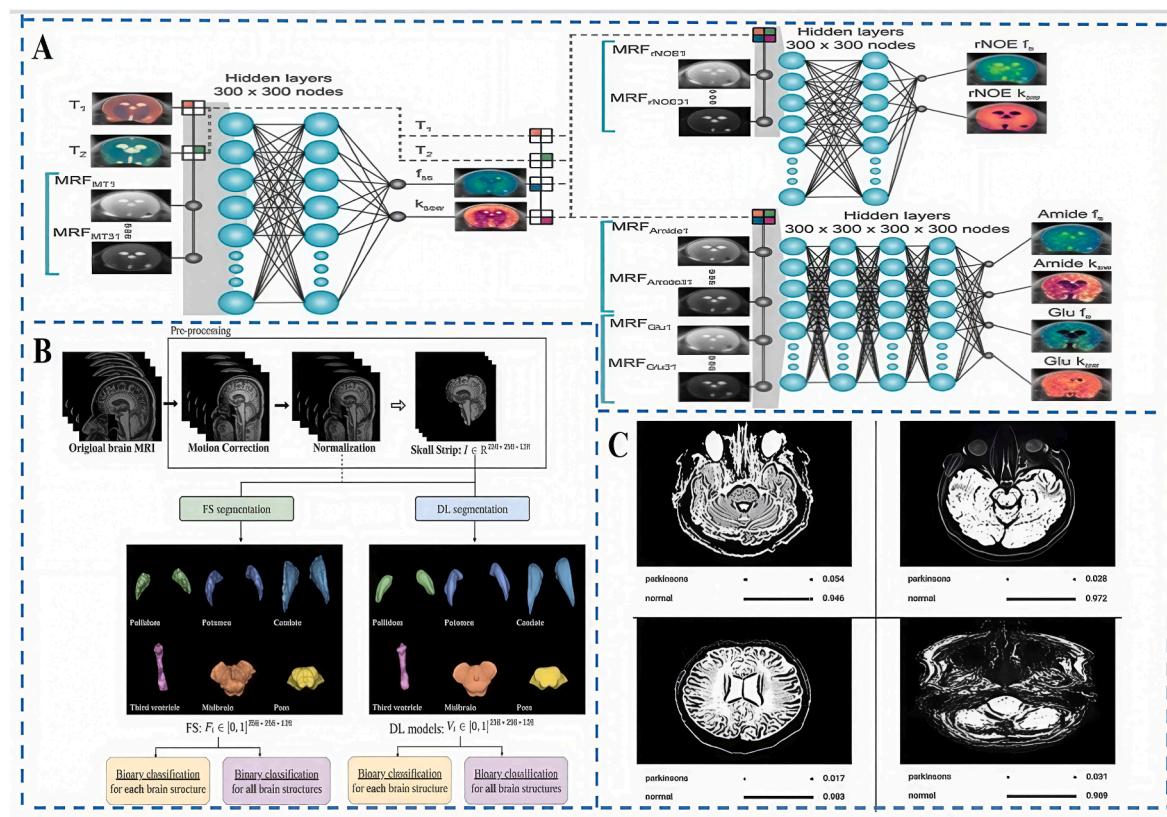


Fig. 11. (A) A deep learning pipeline for multi-metabolite CEST-MRF employs four rapid pulse sequences to generate MT, rNOE, amide, and glutamate images, which together with T1/T2 maps are processed through neural networks to yield quantitative volume fraction and exchange rate maps [82]. (B) The diagnostic performance for Parkinsonian syndromes was compared between deep learning models and FreeSurfer, showing faster analysis and higher accuracy in structural extraction and segmentation [84]. (C) CNN-based assessment of normal brain MRI scans highlights symmetrical morphology, distinct gray–white matter contrast, preserved ventricular size, and absence of atrophy, with probability scores (e.g., 0.946) reflecting the model’s classification confidence [85].

infrastructure to detect freezing of gait (FoG) in real time and provide electrical stimulation interventions. By combining CNNs, SVMs, and Swin Transformer models, the platform achieved high sensitivity in distinguishing FoG from normal gait, supporting at-home rehabilitation [100]. Similarly, multimodal algorithms combining eye-tracking glasses, inertial sensors, and YOLOv8-based object detection enriched fall-risk assessment by accounting for both patient gaze and environmental hazards. With a mean average precision (mAP50) of 0.81, this system demonstrates the value of contextual data in ecological monitoring [101].

To overcome the limitations of single-sensor devices, the IMAS system was designed as a multimodal big data framework capable of predicting clinical scores such as UPDRS-III. Its modular architecture ensures adaptability to emerging sensors, while fusion of sensor-derived and clinical metrics improves interpretability for physicians [102]. Novel sensing technologies are also being explored: a hydrogel-based optical fiber sensor (PAM/SA-Ca²⁺ HOWS) demonstrated high stability, durability, and wireless signal transmission, making it suitable for rehabilitation scenarios and neuromotor monitoring [103].

For device-assisted therapies, such as continuous dopaminergic infusions or DBS, AI-based candidate screening tools have shown promise. A comparative evaluation of CatBoost, SVM, and logistic regression algorithms identified CatBoost as the most effective, achieving AUC values of 0.95 and maintaining 91 % sensitivity even in advanced-stage patients. These results suggest that AI can refine patient selection, minimizing treatment delays and improving outcomes [104].

In synthesis, auxiliary AI applications are reshaping the continuum of PD management, from optimizing clinical workflows to enhancing rehabilitation and supporting therapeutic decision-making. The

convergence of multimodal sensing, advanced machine learning, and interpretability frameworks is paving the way for highly individualized care. Future efforts should prioritize integration of these systems into standard clinical pathways, with a focus on transparency, scalability, and validation in real-world healthcare settings.

4.2.3. Drug-assisted development

Artificial intelligence is being applied with increasing frequency in pharmacological research on PD, especially in areas where conventional strategies have struggled to advance. A clear example is the LRRK2 kinase, mutations of which are strongly implicated in both familial and sporadic forms of the disease. Yet, current inhibitors suffer from limited selectivity, poor pharmacokinetics, and insufficient penetration across the blood–brain barrier. By applying deep learning tools that combine structural modeling with multi-parameter screening, researchers have been able to explore chemical space more efficiently and identify compounds with improved selectivity and drug-like properties [105].

Another direction concerns the regulation of mitochondrial quality control. The kinase PINK1 is central to mitophagy and the clearance of damaged mitochondria, and its upregulation has been suggested as a strategy to reduce neuronal stress in PD. Machine learning models have been used to search for compounds capable of enhancing PINK1 expression among FDA-approved drugs. This kind of drug repurposing not only reduces the time required for clinical entry but also offers a practical route for testing mitochondrial protection as part of PD therapy [106].

Despite these advances, there are important issues that remain unresolved. Most protocols focus on algorithmic performance rather than clinical translation, and the datasets available for training are often too

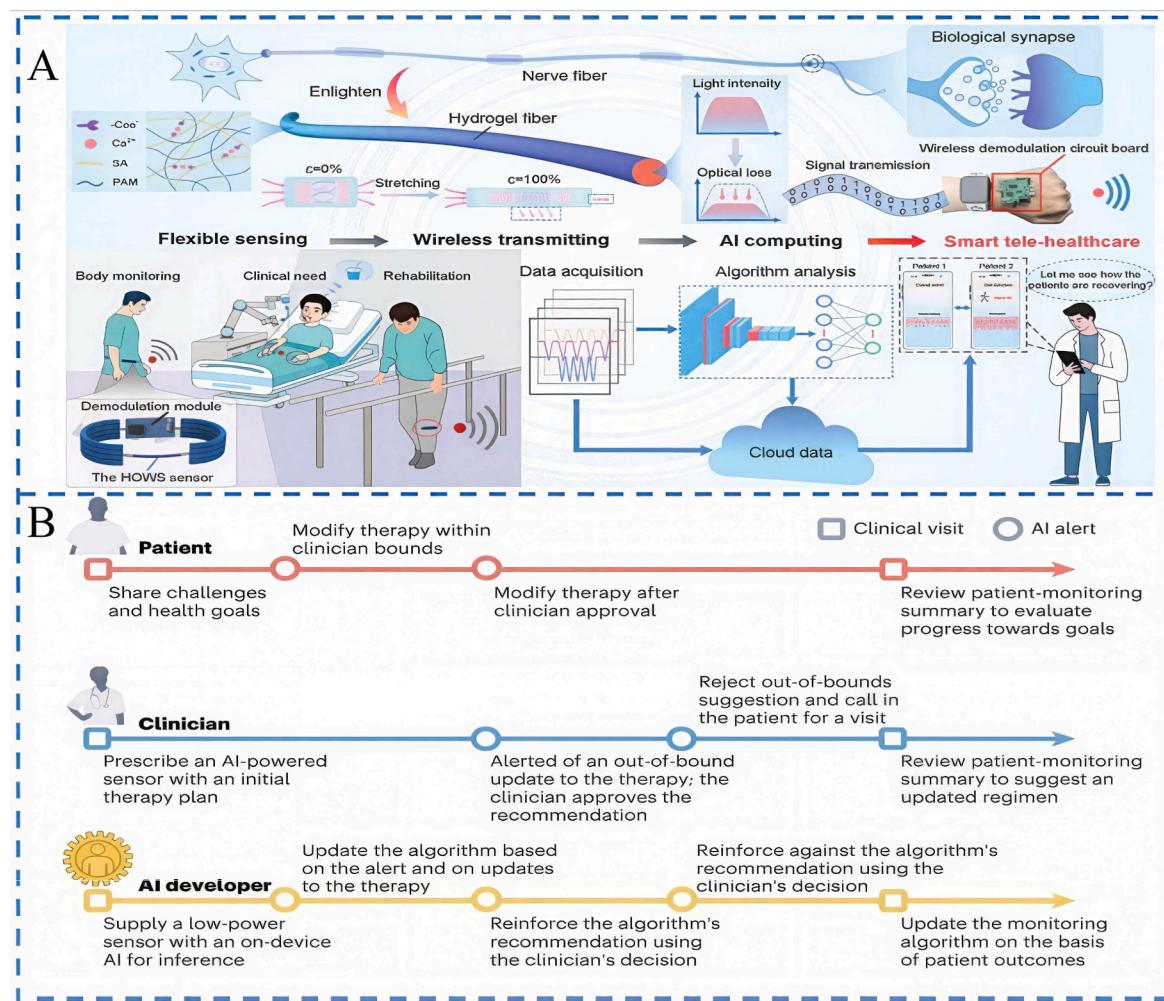


Fig. 12. (A) Schematic illustration of the HOWS sensor, showing its structural design, operational mechanism, and application modes. The figure depicts the inspiration framework, sensing principle, and hydrogel-based optical fiber waveguide with labeled constituents, along with an actual image of the fabricated demodulation circuit board at the lower right. Integrated sensing, wireless data transfer, and AI-assisted computation are also represented [103]. (B) Chronological overview of ClinAIOps implementation in CTM, highlighting the respective contributions of patients, healthcare providers, and AI developers. The integration of continuous health monitoring with information on dosage and administration enables adaptive, data-driven optimization of therapeutic outcomes [98].

limited in size and diversity to represent the full spectrum of disease. This creates the risk of biased predictions that may fail in underrepresented patient populations [107]. There is also a methodological concern: pharmacological state can influence biosignals such as EEG, and AI models may inadvertently capture drug-related patterns instead of genuine disease features, which undermines their reliability in practice [108]. In addition, the adoption of such tools in clinical workflows depends on their compatibility with existing systems and the willingness of medical staff to integrate them into decision-making.

Future research needs to address several aspects in parallel: the creation of larger and more diverse datasets, better strategies to distinguish disease-related information from drug-induced signals, and the incorporation of pharmacokinetic and pharmacodynamic parameters into model training. At the same time, data privacy and ethics must be handled carefully, through anonymization, informed consent, and transparent governance of patient information. If these issues can be resolved, AI-based approaches could become a practical extension of pharmacological research, enabling the refinement of LRRK2 and PINK1 therapies and supporting the development of targeted interventions in PD.

5. AI-driven innovation in MOF/COF material design

As a neurodegenerative disease driven by multiple pathological mechanisms, PD has two core clinical bottlenecks: delayed early diagnosis and limited therapeutic efficacy. The integration of artificial intelligence with materials science has opened an entirely new paradigm for rational material discovery and optimization, and supply the new solutions to the bottlenecks. Traditional strategies for designing functional materials, particularly in the biomedical domain, have largely depended on empirical EXPLOR and incremental trial and error. While these methods have produced important advances, they are inefficient when confronted with the immense chemical and structural diversity available in reticular frameworks such as MOFs and COFs. In the context of PD, where therapeutic requirements demand precise molecular recognition, controlled release, and high biocompatibility, AI provides a transformative pathway for accelerating innovation in framework-based materials [41,114].

The concept of network chemistry, which links molecular building blocks into extended crystalline architectures, naturally creates a vast combinatorial design space. Exploring this landscape experimentally is neither practical nor scalable, as the number of possible linkers, metals, and topologies rapidly exceeds manageable limits. AI methods circumvent these obstacles by applying algorithms capable of mining literature,

extracting patterns from chemical databases, and guiding automated synthesis workflows. Through machine learning and natural language processing, AI systems can identify promising structural motifs, predict functional properties, and iteratively refine designs in ways that are unattainable with conventional methods.

5.1. Drug delivery system

One of the central clinical challenges in PD is the limited therapeutic efficacy, especially the achieving reliable delivery of therapeutic agents to specific regions of the brain. The incorporation of AI into MOF and COF design provides a strategic advantage for addressing this issue. Jiang et al. demonstrated that predictive models integrating descriptors such as particle size, surface charge, and physicochemical properties could estimate the likelihood of framework-based carriers crossing the blood–brain barrier (BBB). These predictions not only streamline material screening but also enable rational tuning of framework structures to enhance BBB permeability and therapeutic precision [109].

Another advance has been the convergence of AI with three-dimensional printing. Yang et al. illustrated that patient-specific data derived from multi-omics analyses can be processed by AI algorithms to determine the optimal architecture of drug carriers. The structural design, once predicted, can then be realized through additive manufacturing, allowing fabrication of delivery systems with highly controlled release profiles that align with individual patient physiology [110]. Cyclodextrin-based MOFs (CD-MOFs) represent another area where AI has proven valuable. Their translation into clinical use has been hindered by difficulties in large-scale synthesis and cost management. Bello and colleagues argued that combining continuous-flow synthesis with AI-optimized process control could significantly reduce production barriers, offering a route toward consistent, scalable, and economically viable manufacturing [111]. Liu et al., working in the area of bone tumor therapy, also emphasized that the integration of AI-driven optimization with MOF and COF carriers will enable not only higher delivery precision but also personalization of treatment regimens. By aligning framework design with patient-specific requirements, these systems could extend beyond oncology into PD therapy, offering adaptive delivery strategies tailored to disease stage and individual metabolic profiles [116–121].

5.2. Material selection

Designing high-performance frameworks requires balancing multiple parameters such as stability, catalytic activity, loading efficiency, and scalability, many of which are interdependent or even conflicting. Single-objective optimization approaches cannot capture this complexity. Multi-agent AI architectures now provide an effective solution by distributing tasks between strategic planning agents and specialized computational modules. Using such systems, a large-scale evaluation of over 12,000 candidate MOF structures identified Y-ABTC as a material that optimally balanced adsorption efficiency, catalytic activity, and process scalability [112].

Advanced deep learning models are further extending predictive accuracy. The Deep Attention Dense Connection Convolution (ADCC) framework integrates chemical and physical descriptors to forecast MOF performance with near-perfect correlation to experimental results. In hydrogen storage applications, this model achieved R^2 values of 0.9886 for volumetric and 0.9982 for gravimetric capacity. Importantly, interpretability analysis revealed that metrics such as void fraction and metal content are decisive in governing performance, offering actionable insights into the structure–function relationship [115].

Reverse design approaches are also redefining material discovery. Rather than screening existing structures, these methods employ evolutionary algorithms and surrogate machine learning models to generate frameworks that directly satisfy desired performance metrics. Using this strategy, ZIF structures with diffusion coefficients surpassing

industrial benchmarks were successfully created, underscoring the feasibility of designing frameworks from performance requirements backward [113]. Large language models (LLMs) now contribute an additional layer of capability in the screening process. By combining retrieval-augmented generation (RAG) with chemical knowledge bases, LLMs can automatically extract synthesis conditions, performance data, and structure–property correlations from the literature. When coupled with external computational tools, these systems offer near-complete automation of the design pipeline, from hypothesis generation through performance prediction [114]. This integration highlights a shift toward an era where materials discovery is no longer limited by manual EXPLOR but is guided by continuous, adaptive, and data-driven refinement.

5.3. Clinical translation pathways

The transformative potential of AI integrated MOF and COF platforms for PD will remain unrealized unless the translation gap between preclinical studies and clinical deployment is addressed. During phase I, where safety and pharmacokinetics are evaluated, AI supported patient selection is important for reducing early safety risks. In phase II, AI allows accurate stratification according to disease subtype and progression rate, so that the study population matches the intended indication of the MOF or COF system. In phase III, AI facilitates trial coordination and multidimensional data analysis across multi center clinical sites.

Successful clinical translation also requires industrial scale production that preserves the structural control achieved during laboratory synthesis. This objective can be supported by AI aided process engineering and supply management. Smart manufacturing systems that employ AI guided additive fabrication can compensate for variations in precursor ink viscosity and maintain consistent microsphere size and drug loading in patient specific batches. AI based supply chain models can predict shortages of starting materials and adjust inventory through demand forecasting linked to clinical recruitment timelines. These strategies collectively provide a pathway to controlled, scalable, and reliable deployment of AI driven MOF or COF systems for PD therapy.

The integration of MOF and COF platforms with AI engenders a synergistic hardware support + intelligent optimization system. MOFs and COFs, defined by high porosity, predictable pore topology, and chemically tailorable surfaces, serve as high performance matrices for molecular sensing and controlled therapeutic transport. AI methodologies address central limitations related to low efficiency in material discovery and non personalized diagnostic or treatment strategies. In combination, these capabilities allow technical constraints in separate material science or biomedical informatics fields to be bypassed. The convergence of artificial intelligence with MOF and COF chemistry is advancing rational design principles and translational deployment pathways for functional frameworks in PD. By accelerating drug-carrier design, guiding multi-objective material selection, and enabling reverse engineering of structures from desired performance, AI is helping to transcend the limitations of empirical trial and error. Importantly, the ability of advanced models to extract mechanistic insights, rather than only predictions, provides a deeper understanding of how pore geometry, surface chemistry, and electronic features dictate therapeutic efficacy. While challenges remain in terms of data standardization, experimental validation, and integration into clinical practice, the trajectory is clear: AI-driven strategies are transforming reticular materials into adaptable, precision-engineered platforms capable of advancing both fundamental research and translational medicine.

In summary, AI assisted covalent organic frameworks have the potential to transform therapeutic strategies for PD. AI based prediction of COF physicochemical properties such as particle size and surface charge can improve blood brain barrier penetration and support site specific delivery to neural tissue. Integrating patient derived multi omics information enables design of personalized COF architectures and fabrication through three dimensional printing for controlled drug release. AI

optimized continuous flow synthesis provides a pathway to scalable and cost effective production. Tailored to disease stage and metabolic state, these intelligent COF systems offer precise and adaptable drug administration, address major obstacles in PD treatment, and support advancement of personalized clinical care.

6. Summary and future outlook

This review has examined the urgent challenges of Parkinson's disease (PD) management, a progressive neurodegenerative disorder with multifactorial pathology, through the lens of advanced reticular materials and computational intelligence. By focusing on the applications of metal–organic frameworks (MOFs), covalent organic frameworks (COFs), and artificial intelligence (AI), then combine the AI with MOFs/COFs, we have highlighted how these innovations are reshaping strategies for early diagnosis, precise monitoring, and therapeutic intervention.

MOFs, with their crystalline tunability and high porosity, have demonstrated significant promise in biosensing and therapy. Their ability to detect trace biomarkers such as dopamine and α -synuclein with nano-molar sensitivity illustrates their potential to overcome the limitations of traditional diagnostic assays. In drug delivery, MOFs can encapsulate and release therapeutic molecules in a controlled fashion, alleviating issues of bioavailability and systemic toxicity. Importantly, the integration of AI with MOF design is beginning to shift this field from empirical discovery toward predictive, precision-oriented engineering.

COFs add a complementary dimension. Their covalently bonded, highly ordered networks offer superior stability and design flexibility, enabling applications ranging from real-time neurotransmitter monitoring to vector platforms for gene therapy. Yet, limitations in physiological stability and clinical translation remain. Addressing these will require innovations in surface modification, biocompatibility enhancement, and hybridization with responsive nanomaterials.

Artificial intelligence is emerging as the connective tissue that links materials science with clinical medicine. The combination of MOF/COF materials and AI technology forms a complementary “hardware support + intelligent optimization” system contribute the development of PD's treatment. Nonetheless, the utility of AI will depend on overcoming issues of limited, homogeneous datasets, ensuring interpretability for clinicians, and embedding strong ethical and privacy safeguards.

Looking ahead, three converging priorities can be clearly defined for the integration of MOF and COF systems with AI in PD therapy. First, in terms of biosafety, AI can utilize high-throughput virtual screening to predict the *in vivo* degradation products, immunogenicity, and long-term toxicity of MOF/COF materials, thereby significantly reducing the cost and risk of *in vitro* experiments. In large-scale production, AI can optimize synthesis process parameters and ensure consistency in batch production of MOFs/COFs through real-time monitoring and feedback regulation. Second, AI-enhanced discovery pipelines should leverage machine learning not only to predict structure–function relationships in frameworks but also to simulate *in vivo* pharmacodynamics and optimize clinical trial design. AI can integrate clinical data, material performance parameters, and regulatory requirements to construct multi-dimensional predictive models, accurately identifying critical barriers for MOFs/COFs transitioning from the laboratory to the clinic in the future. Third, synergistic integration is essential: AI can accelerate the discovery of next-generation frameworks, while MOFs and COFs generate high-quality biomedical data that improve the robustness of AI models. Also, AI models can predict the optimal material pore size, type of functional group modification, and drug release kinetics, enabling MOF/COF carriers to achieve precise targeted delivery. Additionally, combining real-time physiological data monitored by wearable devices, AI can dynamically adjust treatment regimens, advancing personalized PD therapy from theory to practice. Together, this reciprocal feedback loop has the potential to redefine both materials innovation and digital medicine.

Hence, the convergence of MOFs, COFs, and AI is more than an incremental improvement; it signals a paradigm shift in PD research and therapy. These tools allow us to envision a future where diagnostic platforms can sense molecular changes in real time, where drug carriers adaptively release therapeutics in response to pathological triggers, and where predictive algorithms guide treatment choices tailored to individual patients. Such an integrated ecosystem would not merely extend symptomatic relief but could fundamentally alter disease trajectories by targeting PD at multiple pathological levels simultaneously. Realizing this vision will require interdisciplinary collaboration across chemistry, computational science, and clinical research, together with the development of standardized datasets that correlate MOF and COF material characteristics with AI model predictions and resulting clinical outcomes. This need for mechanism based, computational experimental integration parallels successful approaches in related disciplines. In electrocatalysis, for example, the combined use of density functional theory calculations and *in situ* spectroscopic techniques has been central to identifying reactive intermediates at the interface between material and electrolyte, which in turn has informed the rational design of high activity catalytic systems [130,131]. Applying a similarly rigorous and unified framework, where AI based simulations are linked with real time biomedical measurements and incorporated into iterative MOF or COF design, will be crucial for advancing intelligent platforms for PD diagnosis and therapy. If achieved, this convergence could transform PD from a disease managed by symptomatic interventions into one addressed through precision diagnostics and adaptive therapeutics. The AI-guided MOF/COF systems can deliver targeted, adaptive, and safe therapies, marking a decisive leap forward in how we diagnose, treat, and ultimately mitigate the burden of Parkinson's disease, offering a new horizon of hope for patients and clinicians alike.

CRediT authorship contribution statement

Chunyue Shi: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Yan Liang:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Yusheng Wang:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Xinyi Zhang:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Aparna Kushwaha:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Abhinav Kumar:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Data curation, Conceptualization. **Jun Wang:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Qin Ouyang:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Data curation, Conceptualization. **Yong Huang:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Data curation, Conceptualization.

Declaration of competing interest

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

Acknowledgement

This work was supported the Dongguan Social Development Science and Technology Project (20231800936222), Special Funds for Scientific Technological Innovation of Undergraduates in Guangdong Province (pdjh2025bk101, pdjh2024a182), National College Students' Innovation and Entrepreneurship Training Program (202510571003, 202510571014, S202510571082, S202510571097, S202510571112), Guangdong Medical Scientific Research Found (B2025561) and Basic

Science Technology Innovation Project of Guangdong Medical University (4SG2521P, 4SG25146G, 4SG25147G, 4SG25137G, 4SG25328G). Guangdong Medical University Undergraduate Innovation and Entrepreneurship Education Base Project (JDXM2024097, JDXM2024132, JDXM2024168 and JDXM2024140). Dr. Shi thanks for the Shandong Agriculture and Engineering University Start-Up Fund for Talented Scholars (BSQJ202319).

Data availability

The authors do not have permission to share data.

References

- [1] W.E. Xie, Y. Yin, R. Gu, J. Xu, X. Su, Y. Wang, R. Liu, X. Liu, J. Huang, Label-free and highly selective MOFs-based dopamine detection in urine of Parkinson's patients, *Chem. Eng. J.* 443 (2022) 136371.
- [2] H. Chen, S. Guo, Z. Zhuang, S. Ouyang, P. Lin, Z. Zheng, Y. You, X. Zhou, Y. Li, J. Lu, N. Liu, J. Tao, H. Long, P. Zhao, Intelligent identification of cerebrospinal fluid for the diagnosis of parkinson's disease, *Anal. Chem.* 96 (2024) 2534.
- [3] L. Zhou, R. Yang, X. Li, N. Dong, B. Zhu, J. Wang, X. Lin, Su, COF-coated microelectrode for space-confined electrochemical sensing of dopamine in parkinson's disease model mouse brain, *J. Am. Chem. Soc.* 145 (2023) 23727.
- [4] N. Dong, R. Yang, X. Li, B. Zhu, Z. Zhao, J. Cao, J. Wang, X. Lin, L. Zhou, B. Su, A covalent organic frameworks based sensor for adsorptive stripping voltammetric detection of nanomolar dopamine in living mouse brain, *Sens. Sens. Actuator B - Chem.* 426 (2025) 137037.
- [5] A. Zhao, Y. Liu, X. Yu, X. Xing, Artificial intelligence-enabled detection and assessment of Parkinson's disease using multimodal data: a survey, *arXiv* 2502 (2025) 103175.
- [6] J. Valerio, G.A. Vera, M.-F. Gomez, J. Zumaeta, A.M. Alvarez-Pinzon, AI-Driven advances in parkinson's disease neurosurgery: enhancing patient selection, trial efficiency, and therapeutic outcomes, *Brain Sci.* 15 (2025) 494.
- [7] R.F. Mendes, F. Figueira, J.P. Leite, L. Gales, F.A. Almeida Paz, Metal–organic frameworks: a future toolbox for biomedicine? *Chem. Soc. Rev.* 49 (2024) 9121.
- [8] F.L. Liang, D.Y. Ma, L. Qin, Q.Q. Yu, J. Chen, R.X. Liang, C.H. Zhong, H. Liao, Z. Y. Peng, *In situ* generated 2,5-pyrazinedicarboxylate and oxalate ligands leading to a Eu-MOF for selective capture of C_2H_2 from C_2H_2/CO_2 , *Dalton Trans.* 53 (2024) 10070–10074.
- [9] B. R Bloem, M. S. Okun, C. Klein, Parkinson's disease, *Lancet*, 397(10291) 2284.
- [10] D.Y. Ma, T.W. Liang, J.C. Zheng, G.Q. Chen, Y.N. Ye, A. Nezamzadeh-Ejhieh, L. Lu, Z.J. Song, Y. Huang, MOF-based platforms on diabetic disease: advanced and prospect of effective diagnosing and therapy, *React. Funct. Polym.* 218 (2026) 106520.
- [11] T.C. Napier, A. Kirby, A.L. Persons, The role of dopamine pharmacotherapy and addiction-like behaviors in Parkinson's disease, *Prog. Neuropsychopharmacol. Biol. Psychiatry* 102 (2020) 109942.
- [12] H. Zhao, H.Y.-H. Bai, H. Yu, Y.-M. Hu, A rapid method for the determination of dopamine in porcine muscle by pre-column derivatization and HPLC with fluorescence detection, *JPA* 1 (2011) 208.
- [13] Bernardo Patella, et al., Electrochemical detection of dopamine with negligible interference from ascorbic and uric acid by means of reduced graphene oxide and metals-NPs based electrodes, *Anal. Chim. Acta* 1187 (2021) 339124.
- [14] J. Jiang, D. Ding, J. Wang, X. Lin, G. Diao, Three-dimensional nitrogen-doped graphenebased metal-free electrochemical sensors for simultaneous determination of ascorbic acid, dopamine, uric acid, and acetaminophen, *Analyst* 146 (2021) 964.
- [15] C. Chen, J. Ren, P. Zhao, J. Zhang, Y. Hu, J. Fei, A novel dopamine electrochemical sensor based on a β -cyclodextrin/Ni-MOF/glassy carbon electrode, *Microchem. J.* 194 (2023) 109328.
- [16] P. Yan, Z.S. Chen, X. Li, F.L. Liang, Y. Tan, Y.D. Lin, K.Q. Yang, C.X. Xiao, J. H. Wu, D.Y. Ma, Tuning the CO_2 selective adsorption performance in MOFs by incorporating functional groups on the isophthalate skeleton, *J. Solid State Chem.* 330 (2024) 124461.
- [17] J. Xiao, C. Fan, T. Xu, L. Su, X. Zhang, An electrochemical wearable sensor for levodopa quantification in sweat based on a metal–organic framework/graphene oxide composite with integrated enzymes, *Sens. Sens. Actuator B - Chem.* 359 (2022) 131586.
- [18] Y. Wang, Y. Qian, L. Zhang, Z. Zhang, S. Chen, J. Liu, X. He, Y. Tian, Conductive metal–organic framework microelectrodes regulated by conjugated molecular wires for monitoring of dopamine in the mouse brain, *J. Am. Chem. Soc.* 145 (2023) 2118.
- [19] M. Su, W. Peng, Z. Ding, Y. Zhou, H. Gao, Q. Jiang, C. Yu, Multi-walled carbon nanotubes-metal–organic framework nanocomposite based sensor for the monitoring of multiple monoamine neurotransmitters in living cells, *Bioelectrochemistry* 160 (2024) 108776.
- [20] K. Amarnath, T.S. Gopal, A.-J. Malathi, S. Pandiaraj, et al., Electrochemical detection of dopamine and uric acid with annealed metal–organic Framework/MXene ($CuO/C/Ti_3C_2Tx$) nanosheet composites for neurotransmitter sensing, *ACS Appl. Nano Mater.* 8 (2025) 12661.
- [21] H. Ghaedamini, S. Duanghathaipornsuks, P. Onusko, A.M. Binsheheween, D.-S. Kim, Reduced glutathione-modified electrode for the detection of Hydroxyl free radicals, *Biosensors* 13 (2023) 254.
- [22] A. Rezaiezadeh, A. Hajializade, Modified carbon paste electrode using MIL-101 (Fe) metal-organic framework and ionic liquid for ferrocene-mediated voltammetric determination of glutathione, *Anal. Bioanal. Electrochem.* 17 (2025) 190.
- [23] R. Zaibashi, N. Salarizadeh, M.B. Askari, Electrochemical oxidation of glutathione in the presence of tryptophan at carbon paste electrode modified with ni-zn-metal-organic Frameworks/Graphene oxide and ferrocene derivative, *J. Electrochem. Soc.* 171 (2024) 107518.
- [24] Q. Wu, R. Tan, X. Mi, Y. Tu, Electrochemiluminescent aptamer-sensor for alpha synuclein oligomer based on a metal– organic framework, *Analyst* 145 (2020) 2159.
- [25] X. Tan, P. Zhang, C. Ye, Y. Min, Q. Li, Y. Wang, Signal-on photoluminescent detection of dopamine with carbon dots-MnO₂ nanosheets platform based on inner filter effect, *Dyes Pigments* 180 (2020) 108515.
- [26] F. Moghzi, J. Soleimannejad, E.C. Sanudo, J. Janczak, Dopamine sensing based on ultrathin fluorescent metal–organic nanosheets, *ACS Appl. Mater. Interfaces* 12 (2020) 44499.
- [27] L. Pan, F. Yang, S.o Xu, D. Lin, C. Jiang, Fluorescence sensing probe based on functionalized mesoporous MOFs for non-invasive and detection of dopamine in human fluids, *Talanta* 278 (2024) 126356.
- [28] Y.-B. Miao, H.-X. Ren, Q. Zhong, F.-X. Song, Tailoring a luminescent metal – organic framework precise inclusion of Pt-Aptamer nanoparticle for noninvasive monitoring Parkinson's disease, *Chem. Eng. J.* 441 (2022) 136009.
- [29] H.-L. Chen, R.-T. Li, K.-Y. Wu, P. Hu, Z. Zhang, N.-H. Huang, W.-H. Zhang, J.-X. Chen, Experimental and theoretical validations of a one-pot sequential sensing of Hg^{2+} and biothiols by a 3D Cu-based zwitterionic metal–organic framework, *Talanta* 210 (2020) 120596.
- [30] Y. Gong, Y. Fu, D. Lou, A Eu-MOF-Based fluorescent sensing probe for the detection of Tryptophan and Cu^{2+} in aqueous solutions, *J. Fluoresc.* 35 (2025) 1599.
- [31] X. Wu, P. Zhao, S. Tang, Y. Chen, et al., Metal organic framework-based tricolor fluorescence imprinted sensor for rapid intelligent detection of homovanillic acid, *Microchem. J.* 190 (2023) 108607.
- [32] N.D. Mir, S.S. Hossain, S. Biswas, A recyclable luminescent MOF sensor for On-Site detection of insecticide dinotefuran and anti-parkinson's drug entacapone in various environmental and biological specimens, *Chem. Asian J.* 19 (2024) 00377.
- [33] S. Abbasi-Moayed, G.M. Bagheri, V. Gholipour, S. Sojdeh, Colorimetric detection of L-Dopa via anti-etching of Au nanorods catalyzed by an MIL-88A (Fe)-TMB System, *Anal. Methods* 17 (2025) 6002.
- [34] Y. Chen, H. Cheng, H. Tao, et al., Dual-mode sensing platform based on an iodide ion synergistic covalent triazine frameworks (CTFs) for point-of-care testing (POCT) of acetylcholinesterase, *Anal. Chim. Acta* 1350 (2025) 343836.
- [35] X. Xu, J. Chen, R. Hu, Y. Zhang, H. hen, X. Hu, Z. Zhang, A dual-modality immunosensor for simple and reliable detection of nitrated alpha-synuclein in serum based on silver-coated MOF, *Microchim. Acta* 190 (2023) 196.
- [36] D.W. Dickson, M.D. Neuropathology of parkinson disease, PARKINSONISM RELAT D 46 (2018) S30.
- [37] P.-H. Tong, L. Zhu, Y. Zang, J. Li, X.-P. He, T.D. James, Metal–organic frameworks (MOFs) as host materials for the enhanced delivery of biomacromolecular therapeutics, *Chem. Commun.* 57 (2021) 12098.
- [38] M.X. Wu, Y.W. Yang, Metal-Organic framework (MOF)-based drug/Cargo delivery and cancer therapy, *Adv. Mater.* 29 (2017) 1606134.
- [39] M. Bisaglia, L. Bubacco, Copper ions and parkinson's disease: why is homeostasis So relevant? *Biomolecules* 10 (2020) 195.
- [40] J. Aguilera-Rosas, B.A. García-Martínez, C. Ríos, A. Diaz-Ruiz, J.L. Obeso, C. T. Quirino-Barreda, et al., Copper release by MOF-74(Cu): a novel pharmacological alternative to diseases with deficiency of a vital oligoelement, *RSC Adv.* 14 (2024) 855.
- [41] Z. Han, Y. Yang, J. Rushlow, J. Huo, Z. Liu, Y.-C. Hsu, et al., Development of the design and synthesis of metal–organic frameworks (MOFs) – from large scale attempts, functional oriented modifications, to artificial intelligence (AI) predictions, *Chem. Soc. Rev.* 54 (2025) 367.
- [42] L.-C. Meng, J.-Y. Chen, Z.-M. Feng, Z.-G. Jiang, Z. Jin, C.-H. Zhan, Archimedean heterologous helices in $Ti_{10}Cd_6$ -oxo nanoclusters: double-helical self-assembly and therapeutic application in Parkinson's disease, *Inorg. Chem. Front.* 11 (2024) 3527.
- [43] T. Xiao, H. Ji, X. Shangguan, S. Qu, Y. Cui, J. Xu, NLRP3 inflammasome of microglia promotes A1 astrocyte transformation, neo-neuron decline and cognition impairment in endotoxemia, *BIOCHEM BIOPH RES CO* 602 (2022).
- [44] J. Yang, R. Zhang, H. Zhao, H. Qi, J. Li, J.-F. Li, et al., Bioinspired copper single-atom nanzyme as a superoxide dismutase-like antioxidant for sepsis treatment, *EXPLOR* 2 (2022) 20210267.
- [45] Q. Li, X. Ding, Z. Chang, X. Fan, J. Pan, Y. Yang, et al., Metal–organic framework based nanzyme system for NLRP3 inflammasome-mediated neuroinflammatory regulation in parkinson's disease, *Adv. Healthcare Mater.* 13 (2024) 2303454.
- [46] X. Fan, T. Zhang, X. Ding, Y. Gu, Q. Li, W. Jiang, et al., Bioinspired metal–organic framework nanzyme reinforced with thermosensitive hydrogel for regulating inflammatory responses in parkinson's disease, *Nano Res.* 17 (2024) 858.
- [47] W. Jiang, Q. Li, R. Zhang, J. Li, Q. Lin, J. Li, X. Zhou, X. Yan, K. Fan, Chiral metal–organic frameworks incorporating nanozymes as neuroinflammation inhibitors for managing Parkinson's disease, *Nat. Commun.* 14 (2023) 8137.

- [48] M.C. Malaguti, L. Gios, G. Jurman, The third wheel or the game changer? How AI could team up with neurologists in Parkinson's care, *Park. Relat. Disord.* 134 (2025) 107797.
- [49] P.-K. Zhou, Z. Yu, T. Zeng, C. Zhang, Y. Huang, Q. Chen, et al., Reconfigurable neuromorphic computing using methyl-engineered one-dimensional covalent organic framework memristors, *Nano Lett.* 25 (2025) 5891.
- [50] Q. Ouyang, Y. Rong, G. Xia, Q. Chen, Y. Ma, Z. Liu, Integrating humidity-resistant and colorimetric COF-on-MOF sensors with artificial intelligence assisted data analysis for visualization of volatile organic compounds sensing, *Adv. Sci.* 12 (2025) 2411621.
- [51] Y. Yu, A.M. Karami, Y. Lin, L. Qin, A.N. Albalwi, J. Liu, et al., MOF and COF platforms toward kidney-disease: advanced nanovehicles for effective diagnosing and treatment, *Microchem. J.* 212 (2025) 113534.
- [52] L. Huang, Y. Cai, P. Huang, Z. Liao, Y. Tang, J. Pang, et al., Covalent self-assembled highly sensitive humidity sensing system with wireless communication for plant physiology perception under disease stress, *Chem. Eng. J.* 518 (2025) 164501.
- [53] C. Yang, Y. Pan, H. Yu, X. Hu, X. Li, C. Deng, Hollow crystallization COF capsuled MOF hybrids depict serum metabolic profiling for precise early diagnosis and risk stratification of acute coronary syndrome, *Adv. Sci.* 10 (2023) 2302109.
- [54] D. Gu, L. Zhu, Z. Wang, X. Zhi, M. Liu, S. Ge, et al., Multi-responsive Cascade enzyme-like catalytic nanoassembly for ferroptosis amplification and nanozyme-assisted mild photothermal therapy, *Acta Biomater.* 187 (2024) 366.
- [55] J.-Y. Liu, X.-H. Liu, N.-N. Zhong, Y. Xiao, G.-R. Wang, B. Liu, L.-L. Bu, Barriers in bone tumor treatment: the emerging role of drug delivery systems, *Med. Oncol.* 42 (2025) 294.
- [56] J.E. Valerio, G.d.J. Aguirre Vera, M.P. Fernandez Gomez, J. Zumaeta, A. M. Alvarez-Pinzon, AI-Driven advances in parkinson's disease neurosurgery: enhancing patient selection, trial efficiency, and therapeutic outcomes, *Brain Sci.* 15 (2025) 494.
- [57] F.J. Padilla-Godínez, L.I. Ruiz-Ortega, M. Guerra-Crespo, Nanomedicine in the face of parkinson's disease: from drug delivery systems to nanozymes, *Cells* 11 (2022) 3445.
- [58] J. Wang, L. Zhao, B. Yan, Postsynthetic functionalization of covalent organic frameworks for dual channel fluorescence diagnosis of two indicators related to Parkinson's disease, *Sensor. Actuator. B Chem.* 355 (2022) 131297.
- [59] X.-H. Liang, A.-X. Yu, X.-J. Bo, D.-Y. Du, Z.-M. Su, Metal/Covalent-Organic frameworks-based electrochemical sensors for the detection of ascorbic acid, dopamine and uric acid, *Coord. Chem. Rev.* 497 (2023) 215427.
- [60] N. Dong, R. Yang, X. Li, B. Zhu, Z. Zhao, J. Cao, J. Wang, X. Lin, L. Zhou, B. Su, A covalent organic frameworks based sensor for adsorptive stripping voltammetric detection of nanomolar dopamine in living mouse brain, *Sensor. Actuator. B Chem.* 426 (2025) 137037.
- [61] K. Maru, A. Singh, R. Jangir, K.K. Jangir, Amyloid detection in neurodegenerative diseases using MOFs, *J. Mater. Chem. B* 12 (2024) 4553.
- [62] S. Liu, Y. Chen, X. Cheng, G. Li, Y. Hu, Dual enzyme-mimicking bimetallic MOF for selective SERS detection of L-DOPA in human serum based on cascade catalytic reaction, *Talanta* 294 (2025) 128178.
- [63] F. Lange, D.L. Guarin, E. Ademola, D. Mahdy, G. Acevedo, T. Odorfer, J.K. Wong, J. Volkmann, R. Peach, M. Reich, Computer vision uncovers three fundamental dimensions of levodopa-responsive motor improvement in Parkinson's disease, *npj Parkinson's Dis.* 11 (2025) 140.
- [64] N. Tambasco, M. Romoli, P. Calabresi, Levodopa in parkinson's disease: current status and future developments, *Curr. Neuropharmacol.* 16 (8) (2018) 1239–1252.
- [65] X. Sun, N. Wang, Y. Xie, H. Chu, Y. Wang, Y. Wang, In-situ anchoring bimetallic nanoparticles on covalent organic framework as an ultrasensitive electrochemical sensor for levodopa detection, *Talanta* 225 (2021) 122072.
- [66] R.I. Teleanu, M.D. Preda, A.-G. Niculescu, O. Vladăcenco, C.I. Radu, A. M. Grumezescu, D.M. Teleanu, Current strategies to enhance delivery of drugs across the blood-brain barrier, *Pharmaceutics* 14 (2022) 987.
- [67] J.R. Wu, Y. Hernandez, K.F. Miyasaki, E.J. Kwon, Engineered nanomaterials that exploit blood-brain barrier dysfunction for delivery to the brain, *Adv. Drug Deliv. Rev.* 197 (2023) 114820.
- [68] P. Horcajada, C. Serre, M. Vallet-Regí, M. Sebban, F. Taulelle, G. Ferey, Metal-Organic frameworks as efficient materials for drug delivery, *Angew. Chem. Int. Ed.* 45 (2006) 5974.
- [69] C. Saraiva, C. Praça, R. Ferreira, T. Santos, L. Ferreira, L. Bernardino, Nanoparticle-mediated brain drug delivery: overcoming blood-brain barrier to treat neurodegenerative diseases, *J. Contr. Release* 235 (2016) 1.
- [70] Y. Smith, T. Wichmann, S.A. Factor, M.R. DeLong, Parkinson's disease therapeutics: new developments and challenges since the introduction of levodopa, *Neuropsychopharmacology* 37 (2012) 213.
- [71] V. Tabar, H. Sarva, A.M. Lozano, A. Fasano, S.K. Kalia, K.K.H. Yu, et al., Phase I trial of HES cell-derived dopaminergic neurons for Parkinson's disease, *Nature* 641 (2025) 978.
- [72] J. Yang, F. Kang, X. Wang, Q. Zhang, Design strategies for improving the crystallinity of covalent organic frameworks and conjugated polymers: a review, *Mater. Horiz.* 9 (2022) 121.
- [73] Y. Shi, J. Yang, F. Gao, Q. Zhang, Covalent organic frameworks: recent progress in biomedical applications, *ACS Nano* 17 (2023) 1879.
- [74] A. Halmemies-Beauchet-Filleau, A. Vanhatalo, V. Toivonen, T. Heikkilä, M.R. F. Lee, K.J. Shingfield, Effect of replacing grass silage with red clover silage on nutrient digestion, nitrogen metabolism, and milk fat composition in lactating cows fed diets containing a 60:40 forage-to-concentrate ratio, *J. Dairy Sci.* 97 (2014) 3761.
- [75] L. Yao, Z. Zhou, S. Wang, Q. Zou, H.-X. Wang, L.-X. Ma, S. Wang, X. Zhang, Phosphorylation of covalent organic framework nanospheres for inhibition of amyloid- β peptide fibrillation, *Chem. Sci.* 13 (2022) 5902.
- [76] T. Meng, X. Wang, S. Jiang, S. Chen, S. Zhou, Y. Zhu, J. Wu, D. Hu, Y. Yan, G. Zhang, Delivery of small-molecule drugs and protein drugs by injectable acid-responsive self-assembled COF hydrogels for combinatorial lung cancer treatment, *ACS Appl. Mater. Interfaces* 15 (2023) 42354.
- [77] M. Bisaglia, I. Tessari, S. Mammi, L. Bubacco, Interaction between α -Synuclein and metal ions, still looking for a role in the pathogenesis of parkinson's disease, *Neuromol. Med.* 11 (2009) 239.
- [78] S.A. Rosenberg, P. Aebersold, K. Cornetta, A. Kasid, R.A. Morgan, R. Moen, E. M. Karson, M.T. Lotze, J.C. Yang, S.L. Topalian, M.J. Merino, K. Culver, A. D. Miller, R.M. Blaese, W.F. Anderson, Gene transfer into Humans—immunotherapy of patients with advanced melanoma, using tumor-infiltrating lymphocytes modified by retroviral gene transduction, *N. Engl. J. Med.* 323 (1990) 570.
- [79] K. Hao, Z.P. Guo, L. Lin, P.J. Sun, Y.H. Li, H.Y. Tian, X.S. Chen, Covalent organic framework nanoparticles for anti-tumor gene therapy, *Sci. China Chem.* 64 (2021) 1235.
- [80] T. Li, D.W. Wang, M. Meng, X.Y. Guo, L. Lin, Z.Y. Yang, Z. Li, L.W. Xiang, C. Liu, J. Chen, X. Pang, K. Hao, H.Y. Tian, X.S. Chen, Dual regulation of the orderly aggregation of covalent organic frameworks at the molecular level and nanoscale to achieve efficient phototherapy and gene therapy, *Chem. Eng. J.* 492 (2024) 152163.
- [81] S. Priyadarshini, K. Ramkumar, S. Vairavasundaram, K. Narasimhan, S. Venkatesh, R. Amirtharajan, K. Kotecha, A comprehensive framework for Parkinson's disease diagnosis using explainable artificial intelligence empowered machine learning techniques, *Alex. Eng. J.* 107 (2024) 568.
- [82] H. Shmueli, M. Rivlin, O. Perlman, Quantitative multi-metabolite imaging of Parkinson's disease using AI boosted molecular MRI, *arXiv.physics.med-ph* 2507 (2025) 11329.
- [83] W.J. Li, Q.R. Rao, S.Y. Dong, M.Y. Zhu, Z. Yang, X.G. Huang, PIDGN: an explainable multimodal deep learning framework for early prediction of Parkinson's disease, *J. Neurosci. Methods* 415 (2025) 110363.
- [84] J. Song, J. Hahm, J. Lee, C.Y. Lim, M.J. Chung, J. Youn, J.W. Cho, J.H. Ahn, K. Kim, Comparative validation of AI and non-AI methods in MRI volumetry to diagnose Parkinsonian syndromes, *Sci. Rep.* 13 (2023) 3439.
- [85] S. Reddy, D. Giri, R. Patel, Artificial intelligence diagnosis of parkinson's disease from MRI scans, *Cureus* 16 (2024) e58841.
- [86] I. Karabayır, F. Gunturkun, L. Butler, S.M. Goldman, R. Kamaleswaran, R. L. Davis, K. Colletta, L. Chinthala, J.L. Jeferies, K. Bobay, G.W. Ross, H. Petrovitch, K. Masaki, C.M. Tanner, O. Akbilgilic, Externally validated deep learning model to identify prodromal Parkinson's disease from electrocardiogram, *Sci. Rep.* 13 (2023) 12290.
- [87] J. Wolf, D.K. Rasmussen, Y.J. Sun, A. Dufour, A.G. Bassuk, V.B. Mahajan, Liquid-biopsy proteomics combined with AI identifies cellular drivers of eye aging and disease in vivo, *Cell* 186 (2023) 4868.
- [88] Z.Y. Li, S.Y. Zhang, Q.F. Xiao, S.X. Shui, P.L. Dong, Y.J. Jiang, Y.Y. Chen, F. Lan, Y. Peng, B.W. Ying, Y. Wu, Energy-confinement 3D flower-shaped cages for AI-Driven decoding of metabolic fingerprints in cardiovascular disease diagnosis, *ACS Nano* 19 (2025) 6180.
- [89] X. Xiang, Z.H. Zhang, J. Ma, Y. Deng, AI WALKUP: a computer-vision approach to quantifying MDS-UPDRS in parkinson's disease, *arXiv.cs.AI* 2404 (2024) 01654.
- [90] J.Y. Xu, X. Xu, X.D. Guo, Z.Z. Li, B.Y. Dong, C. Qi, C.H. Yang, D. Zhou, J.L. Wang, L. Song, P. He, S.S. Kong, S.C. Zheng, S.C. Fu, W. Xie, X. Liu, Y. Cao, Y.L. Liu, Y. Q. Qiu, Z.Y. Zheng, F. Yang, J. Gan, X. Wu, Improving reliability of movement assessment in Parkinson's disease using computer vision-based automated severity estimation, *J. Parkinsons Dis.* 15 (2025) 349.
- [91] A. Aljohani, Late feature fusion using neural network with voting classifier for Parkinson's disease detection, *BMC Med. Inf. Decis. Making* 24 (2024) 269.
- [92] M. Ianculescu, C. Petean, V. Sandulescu, A. Alexandru, A.-M. Vasilevscu, Early detection of parkinson's disease using AI techniques and image analysis, *Diagnostics* 14 (2024) 2615.
- [93] S. Zhao, J.L. Zhang, J.B. Zhang, Predicting UPDRS in Parkinson's disease using ensembles of self-organizing map and neuro-fuzzy, *J. Cloud Comput.* 13 (2024) 83.
- [94] S.T. Arasteh, C.D. Rios-Urrego, E. Noeth, A. Maier, S.H. Yang, J. Rusz, J. R. Orozco-Arroyave, Federated learning for secure development of AI models for Parkinson's disease detection using speech from different languages, *arXiv.cs.LG* 2305 (2023) 11284.
- [95] M. Parsapoor, Synthetic data generation techniques for developing AI-based speech assessments for parkinson's disease (A comparative study), *arXiv.cs.LG* 2312 (2023) 02229.
- [96] B. Demir, S.A. Altuntaş, İ. Kurt, S. Ulukaya, O. Erdem, S. Güler, C. Uzun, Cognitive activity analysis of Parkinson's patients using artificial intelligence techniques, *Neurol. Sci.* 46 (2025) 147.
- [97] M. Rashik, S. Sweth, N. Agrawal, S. Kochar, K.M. Smith, F. Rajabiyazdi, V. Setlur, N. Mahyar, A. Sarvghad, AI-Enabled conversational journaling for advancing parkinson's disease symptom tracking, *arXiv.cs.HC* 2503 (2025) 03532.
- [98] E. Chen, S. Prakash, V.J. Reddi, D. Kim, P. Rajpurkar, A framework for integrating artificial intelligence for clinical care with continuous therapeutic monitoring, *Nat. Biomed. Eng.* 9 (2025) 445.
- [99] N. Haliasos, D. Giakoumettis, P. Gnanaratnasingham, H.L. Low, A. Misbahuddin, P. Zikos, V. Sakkalis, S. Cleo, A. Vakis, S. Bisdas, Personalizing deep brain stimulation therapy for parkinson's disease with Whole- brain MRI radiomics and machine learning, *Cureus* 16 (2024) e59915.

- [100] H. Ghayvat, M. Awais, R. Geddam, M.T. Quasim, S.A. Khowaja, K. Dev, AiCareGaitRehabilitation: multi-Modalities sensor data fusion for AI-IoT enabled realtime electrical stimulation device for pre-Fog and post-Fog to person with Parkinson's disease, *Inf. Fusion* 122 (2025) 103155.
- [101] J. Moore, Y. Celik, S. Stuart, P. McMeekin, R. Walker, V. Hetherington, A. Godfrey, Using video technology and AI within parkinson's disease free-living fall risk assessment, *Sensors* 24 (2024) 4914.
- [102] L. Dipietro, U. Eden, S. Elkin-Frankston, M.M. El-Hagrassy, D.D. Camsari, C. Ramos-Estebanez, F. Fregni, T. Wagner, Integrating big data, artificial intelligence, and motion analysis for emerging precision medicine applications in Parkinson's disease, *J. Big Data* 11 (2024) 155.
- [103] T.L. Li, Q. Wang, Z.C. Cao, J.L. Zhu, N. Wang, R. Li, W. Meng, Q. Liu, S.F. Yu, X. Q. Liao, A.G. Song, Y.G. Tan, Z.D. Zhou, Nerve-inspired optical waveguide stretchable sensor fusing wireless transmission and AI enabling smart tele-healthcare, *Adv. Sci.* 12 (2025) 2410395.
- [104] E. Freire-Álvarez, I. Legarda Ramírez, R. García-Ramos, F. Carrillo, D. Santos-García, J.C. Gómez-Esteban, J.C. Martínez-Castrillo, I. Martínez-Torres, C. J. Madrid-Navarro, M.J. Pérez-Navarro, F. Valero-García, B. Vives-Pastor, L. Muñoz-Delgado, B. Tijero, C. Morata Martínez, J.M. Valls, R. Aler, I.M. Galván, F. Escamilla-Sevilla, Artificial intelligence for identification of candidates for device-aided therapy in Parkinson's disease: DELIST-PD study, *Comput. Biol. Med.* 185 (2025) 109504.
- [105] X.Q. Gong, S.Y. Tan, Y.W. Yang, Y. Yu, X.J. Yao, H.X. Liu, Development of LRRK2 inhibitors through computational strategies: a promising avenue for Parkinson's disease, *Drug Discov. Today* 30 (2025) 104446.
- [106] J. Haneczok, M. Delijewski, R. Moldzio, AI molecular property prediction for Parkinson's disease reveals potential repurposing drug candidates based on the increase of the expression of PINK1, *Comput. Methods Progr. Biomed.* 241 (2023) 107731.
- [107] M.Y. Zhang, E.Z. Tang, H.W. Ding, Y. Zhang, Artificial intelligence and the future of communication sciences and disorders: a bibliometric and visualization analysis, *Journal of speech, J. Speech Lang. Hear. Res.* 67 (2024) 4369.
- [108] A. Kurbatskaya, F.N. Låder, A.S. Nese, K. Brönnick, A. Fernandez-Quilez, Beyond the signal: medication state effect on EEG-based AI models for parkinson's disease, *arXiv.eess.SP* 2503 (2025) 21992.
- [109] M. Jiang, G.H. Zhang, Q. Zeng, D.S. Xiong, X. Bai, Y. Wu, J. Liu, J. Chen, T. Jiang, W.-X. Liu, Y.-B. Miao, Weaving the gates of life: pioneering a new era in oral gene delivery with metal-organic frameworks, *Chem. Eng. J.* 503 (2025) 158522.
- [110] X. Yang, L.Z. Zhang, Z.L. Zheng, R. Langer, A. Jaklenec, Advanced oral delivery systems for nutraceuticals, *Adv. Healthcare Mater.* 14 (2025) 2500271.
- [111] M.G. Bello, J. Zhang, L. Chen, Cyclodextrin metal-organic framework design principles and functionalization for biomedical application, *Carbohydr. Polym.* 364 (2025) 123684.
- [112] X. Bai, H.-T. Wang, L.-H. Xie, X. Zhang, N. Xing, J.-Y. Zhang, D.-Y. Chen, Z.-H. Xie, L.-F. Ding, J.-R. Li, An integrated AI system for multi-objective screening of MOF materials, *Sep. Purif. Technol.* 376 (2025) 133939.
- [113] P. Krokidas, M. Kainourgiakis, T. Steriotis, G. Giannakopoulos, Inverse design of ZIFs through artificial intelligence methods, *Phys. Chem. Chem. Phys.* 26 (2024) 25314.
- [114] Z. Zheng, N. Rampal, T.J. Inizan, C. Borgs, J.T. Chayes, O.M. Yaghi, Large language models for reticular chemistry, *Nat. Rev. Mater.* 10 (2025) 369.
- [115] A.H. Ba-Alawi, S. Palla, S.R. Ambati, H.-T. Nguyen, S. Kim, C. Yoo, Chemical-guided screening of top-performing metal-organic frameworks for hydrogen storage: an explainable deep attention convolutional model, *Chem. Eng. J.* 498 (2024) 155626.
- [116] J.-Y. Liu, X.-H. Liu, N.-N. Zhong, Y. Xiao, G.-R. Wang, B. Liu, L.-L. Bu, Barriers in bone tumor treatment: the emerging role of drug delivery systems, *Drug Deliv. Transl. Res.* 42 (2025) 1.
- [117] Y. Yang, Y. Yuan, G. Zhang, H. Wang, Y.-C. Chen, Y. Liu, C.G. Tarolli, D. Crepeau, J. Bukartyk, M.R. Junna, A. Videmovic, T.D. Ellis, M.C. Lipford, R. Dorsey, D. Katabi, Artificial intelligence-enabled detection and assessment of Parkinson's disease using nocturnal breathing signals, *Nat. Med.* 28 (2022) 2207–2215.
- [118] M. Hoq, M.N. Uddin, S.-B. Park, Vocal feature extraction-based artificial intelligent model for parkinson's disease detection, *Diagnostics* 11 (2021) 1076.
- [119] Z.-D. Chen, L. Zhao, H.-Y. Chen, J.-N. Gong, X. Chen, C.C. Chen, A novel artificial intelligence protocol to investigate potential leads for parkinson's disease, *RSC Adv.* 10 (2020) 22939.
- [120] S. Grover, S. Bhartia, Akshama, A. Yadav, K.R. S, Predicting severity of parkinson's disease using deep learning, *Procedia Comput. Sci.* 132 (2018) 1788.
- [121] F. Liang, J. Li, Y. Feng, Y. Zhou, L. Cao, D. Omoding, M. R. Jayswal, A. Kumar, Z. J. Song, J. Wang, Advances and prospects in Alzheimer's disease diagnosis and treatment using MOFs and COFs: Mechanism and AI-assisted strategies, *React. Funct. Polym.* 219 (2026) 106601.
- [122] B. Mohan, R. Kumar, Virender, G. Singh, K. Singh, A.J.L. Pombeiro, X.M. Yang, P. Ren, Covalent organic frameworks (COFs) and metal-organic frameworks (MOFs) as electrochemical sensors for the efficient detection of pharmaceutical residues, *Environ. Int.* 175 (2023) 107928.
- [123] B. Mohan, Virender, R.K. Gupta, A.J.L. Pombeiro, A.A. Solovev, G. Singh, Advancements in metal-organic, enzymatic, and nanocomposite platforms for wireless sensors of the next generation, *Adv. Funct. Mater.* 34 (2024) 2405231.
- [124] D.Y. Ma, T.W. Liang, J.C. Zheng, G.Q. Chen, Y.N. Ye, A. Nezamzadeh-Ejhieh, L. Lu, Z.J. Song, Y. Huang, MOF-based platforms on diabetic disease: Advanced and prospect of effective diagnosing and therapy, *React. Funct. Polym.* 218 (2026) 106520.
- [125] B. Mohan, Tuned porous MOFs & COFs for arsenic removal- advanced water remediation approach, *Desalination* 592 (2024) 118075.
- [126] J.Y. Chen, G.X. Xu, R.P. Shen, J.Z. Xu, C.C. Lu, X. Li, Q. Feng, Q. Li, Communications among neurocytes in parkinson's disease regulated by differential metabolism and blood-brain barrier traversing of chiral gold Cluster-MOF integrated nanoparticles, *Adv. Sci.* 12 (2025) 2500026.
- [127] M.B. Alahri, R. Arshadizadeh, M. Raeisi, M. Khatami, M.S. Sajadi, W. K. Abdelbasset, R. Akhmadeev, S. Iravani, Therapeutic applications of metal-organic frameworks (MOFs)-based materials in brain disorders: recent advances and challenges, *Inorg. Chem. Commun.* 134 (2021) 108997.
- [128] Z.S. Han, M.Z.Z. Yuan, N. Nguyen, H.C. Zhou, J.E. Hubbard Jr., Y. Wang, Brain-specific targeted delivery of therapeutic agents using metal-organic framework-based, nanomedicine 514 (2024) 215926.
- [129] Y. Liu, H.H. Hong, J.C. Xue, J.S. Luo, Q. Liu, X.J. Chen, Y. Pan, J.W. Zhou, Z. M. Liu, T.K. Chen, Near-infrared radiation-assisted drug delivery nanoplatform to realize blood-brain barrier crossing and protection for parkinsonian therapy, *ACS Appl. Mater. Interfaces* 13 (2021) 37746–37760.
- [130] L.X. Su, H. Wu, S.N. Zhou, R.J. Qian, C.X. Cui, S.K. Zhang, L.Q. Wu, W.T. Li, H. Pang, Narrowing the kinetic gap between alkaline and acidic hydrogen oxidation reactions through intermediate behaviors regulated on D-p hybridized Pd-Based catalysts, *Adv. Sci.* (2025) e13616.
- [131] L.X. Su, H. Wu, S.K. Zhang, C.X. Cui, S.N. Zhou, H. Pang, Insight into intermediate behaviors and design strategies of platinum group metal-based alkaline hydrogen oxidation catalysts, *Adv. Mater.* 37 (2025) 2414628.
- [132] H. Nabipour, S. Rohani, Metal-organic frameworks for overcoming the blood-brain barrier in the treatment of brain diseases: a review, *Nanomaterials* 14 (2024) 1379.