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Review

# Biosensors in Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is one of the most critical disorders of the elderly and strongly associated with increased disability, and reduced quality of life. PD is a progressive neurodegenerative disease affecting more than six million people worldwide. Evaluation of clinical manifestations, as well as movement disorders by a neurologist and some routine laboratory tests are the most important diagnostic methods for PD. However, routine and old methods have several disadvantages and limitations such as low sensitivity and selectivity, high cost, and need for advanced equipment. Biosensors technology opens up new diagnoses approach for PD with the use of a new platform that allows reliable, repeatable, and multidimensional identification to be made with minimal problem and discomfort for patients. For instance, biosensing systems can provide promising tools for PD treatment and monitoring. Amongst biosensor technology, electrochemical techniques have been at the frontline of this progress, thanks to the developments in material science, such as gold nanoparticles (AuNPs), quantum dots (QDs), and carbon nanotubes (CNTs). This paper evaluates the latest progress in electrochemical and optical biosensors for PD diagnosis.

## 1. Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative syndromes of the elderly with various causes [1]. Today, PD diagnosis virtually is dependent on clinical insight. However, there are not any recognized laboratory tests for specific and reliable PD diagnosis [2]. Besides, the differential diagnosis for PD can be relatively challenging owing to the overlapping symptoms, mainly in its primary stages. Accordingly, there is an essential clinical requirement to improve biosensing tools for PD diagnosis [3,4]. Different and specific biomarkers are the critical point in the development of PD's diagnostic methods. Specific biomarkers are biologically active substances that can influence clinical manifestations and are established by different clinical syndromes [5]. Assessment of the expression patterns of biomarkers is instrumental in all stages of the diagnostic and therapeutic methods [5,6]. Several studies show that some neurotransmitters, alpha-synuclein, and compounds, including 8-hydroxy-2′ -deoxyguanosine (8-OHdG), are among the most vital biomarkers associated with PD. Undoubtedly, accurate identification of biomarkers is vital for PD control and treatment. Numerous routine methods, such as ELISA, western blotting, chromatography, and serology, apply to identifying PD biomarkers [7]. Although routine methods show relatively acceptable results, they face serious challenges, such as high costs, advanced equipment, specialized operators for test performance and result interpretation, low sensitivity, and specificity [8]. Recently, biosensors have been developed as analytical tools to detect and identify a wide range of analytes [9]. The structure simplicity and budget-friendliness, high availability, sensitivity and specificity, and easy execution and interpretation of the results are the imperative features of the biosensors technology [10], which broadly cover the disadvantages of routine methods [11]. Biosensors have been developed in several classes, among which immunosensors and genosensors are of great importance. The main function of immunosensors and genosensors is based on identifying antibodies/antigen complex and specific genes[9]. The material used in the biosensors assembly is an essential determinant of their sensitivity and cost-effectiveness. For instance, graphite compounds increase the system's sensitivity while significantly reducing the costs [12,13]. Moreover, despite their low cost and straightforward structure,

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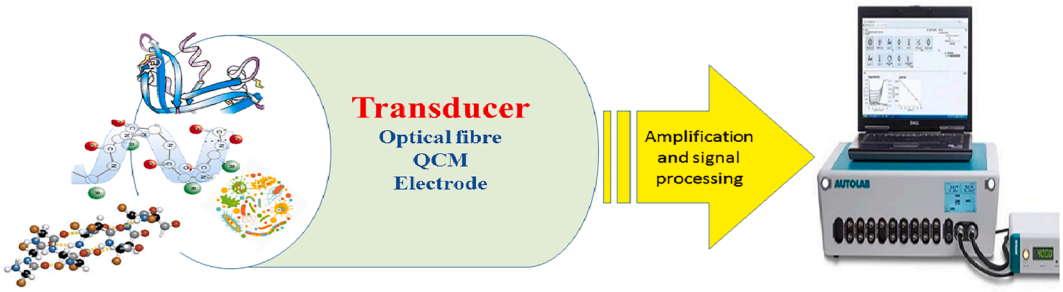


**Fig. 1.** The schematic illustration of the biosensors structure [14].

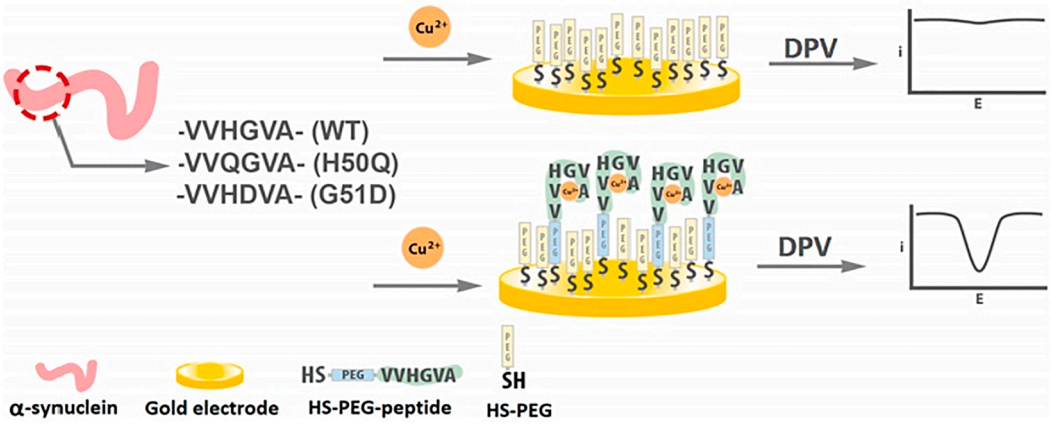


**Fig. 2.** Schematic view of the modification of gold electrode surfaces using HS-PEG and HS-PEG peptides. As the interaction between the peptides and copper (II) ions shows, the electrochemical reduction current signal of copper (II) was only perceived in the presence of peptides on the electrode surface. The hexamer peptides represent the metal-binding region 48–53 of the wild-type (WT) α-syn and its mutants (H50Q and G51D) [40].

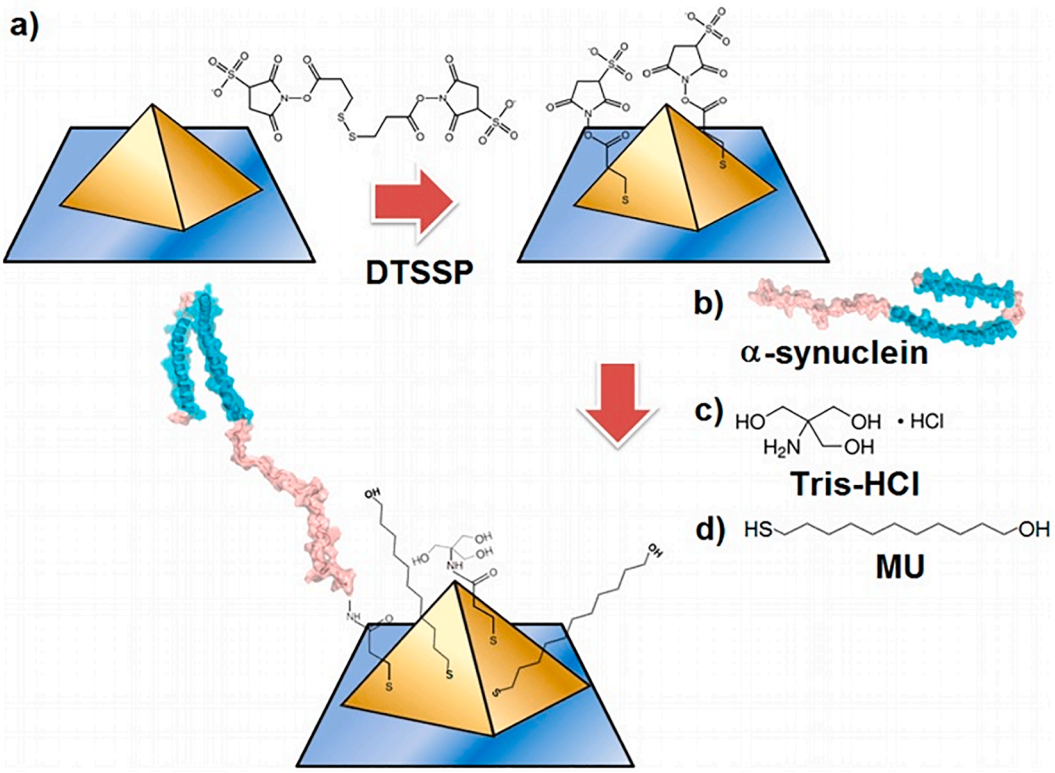


**Fig. 3.** Schematic view of the proposed device, as shown, Sulfosuccinimidil-propionate (DTSSP) was immobilized as a linker for the covalent attachment of (b) a-Syn, The unmodified DTSSP was quenched using (c) Tris-HCl, and the pinholes on the Au-nanopyramids were backfilled using (d) MU [41].

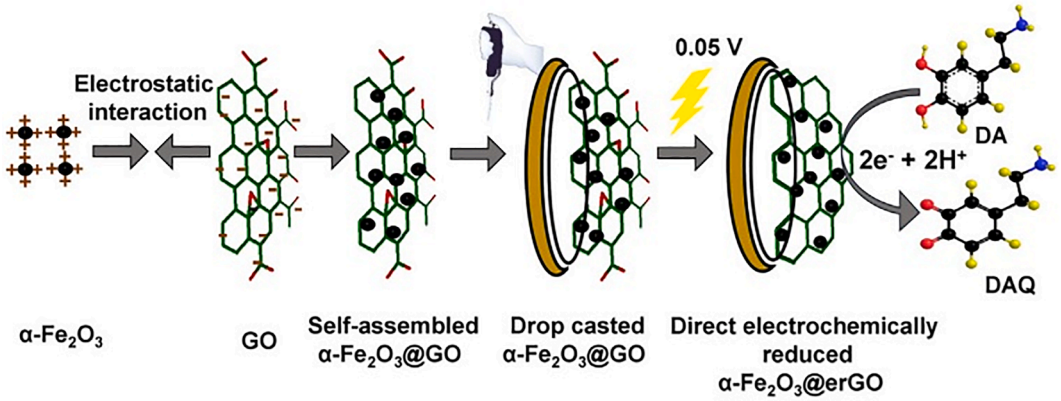


**Fig. 4.** Schematic illustration of the fabrication of α-Fe2O3@erGO modified GCE towards DA, electrochemical reduction of self-assembled, ex-situ synthesized α-Fe2O3 attached GO to erGO (α-Fe2O3@erGO) on glassy carbon electrode (GCE) for selective identification of dopamine (DA), as the primary biomarker of Parkinson's disease [46].

paper-based biosensors represent optimal performance [9].

### 1.1. Biosensors

Biosensors are analytical tools with important features, such as high sensitivity and specificity, low cost, and fast operation. Enzymes, cells, antibodies, and nucleic acids can be measured as sensing bioelements that form a recognition layer combined with a transducer by a blockage via covalent bonding, adsorption, or cross-linking. The schematic illustration of the biosensors structure is shown in Fig. 1 [14].

Many types of biosensors, such as tissue-based, enzyme-based, DNA biosensors, immunosensors, and thermal and piezoelectric biosensors, were developed extensively to detecting various biomarkers. Although several biosensors have been developed for various diseases, surprisingly, just a few biosensing tools have been specifically developed to identify PD-related biomarkers [15] (see Figs. 2 and 3).

The limit of detection (LOD) is a principal performance indicator of an analytical technique. Advancement in analytical chemistry is measurable by the shift of the LOD towards lower values. The emerging picture would reflect only part of the progress [16,17]. In fact, many problems in analytical chemistry are associated with the detection and determination of elements or compounds in small amounts of sample (microanalysis), very low concentrations or small amounts in the larger specimen (trace analysis), or even low concentration determination in the small samples [18]. In most cases, a method is considered very sensitive when the LOD is low, and in many cases, the LOD and sensitivity are considered synonymous [18,19].

## 2. Parkinson's disease biomarkers and developed biosensors

The arrangement of detection approaches for PD-related biomarkers is one of the most reliable ways of advancing PD diagnostic approaches. Many biomarkers can apply to PD diagnosing. For instance, orexin is a vital neuropeptide hormone released by neurons in the dorsolateral hypothalamus and has a vital role in regulating heart rate, hypertension, and sleep-wake cycle. Several studies have shown that orexin concentration in patients with PD is lower than the healthy individuals [20,21]. 8-hydroxy-2′ -deoxyguanosine (8-OHdG) is another PD biomarker candidate produced during DNA oxidization by the reactive oxygen species (ROS). The study results indicated a direct link between oxytocin and PD. Hence, it is crucial to check the oxytocin level for PD monitoring. However, since 8-hydroxy-20-deoxyguanosine is not PD-specific since it is produced by DNA damage; thus, other biomarkers should also be considered [22,23]. Alpha-synuclein, dopamine, and its associated precursor L-DOPA are the potential candidate PD biomarkers used extensively in diagnostics approaches [24,25]. Apolipoproteins are small hydrophobic molecules that have a critical part in several neurodegenerative diseases. For example, ApoD is expressed and secreted from brain and peripheral tissues, and thus, can be potential PD biomarkers [26–28]. Table 1 represents the normal levels of PD-related biomarkers, which can vary depending on patients' age and physiological condition (see Table 2).

**Table 1**
Parkinson-related biomarkers normal ranges in blood.

| Biomarkers | Normal Ranges | Ref |
|---|---|---|
| **a-Syn** | 3.6 (1.5) +/− 1.4 CI 0.8–6.4 (ng/ml) | [29] |
| 8-OHd | 103.44 (48.34) (ng/ml) | [30] |
| Dopamine | 10 ng/ml | [31] |
| Ascorbic acid | 0. 6–2 mg/dL | [32] |
| Uric acid | 2.4–6.0 mg/dL (female) and 3.4–7.0 mg/dL (male) | [33,34] |

**(8-OHdG)**: 8-hydroxy-2′-deoxyguanosine, **(a-Syn):** Alpha-synuclein.

### 2.1. Alpha-synuclein

Protein aggregation is the essential state associated with some neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease; hence, identifying them has diagnostic significance [35]. Originally, Alpha-synuclein (a-Syn) is an unfolded and abundant protein in the brain and the base of Lewy body amyloid nature in PD. Alpha-synuclein consists of 140 amino acids (with a mass of 14.4 kDa) and, mostly expressed in the neural tissue [36,37]. The physiological role of a-Syn is unclear, though its role in synaptic plasticity and synaptic transmission is critical as it enhances transmitter release from the presynaptic terminal. Any aggregation, misfolding, and fibrillation of a-Syn into Lewy bodies leads to acute symptoms in the pathogenesis of PD [38,39]. Based on the findings, a single amino acid mutation affected the peptides, which considerably influenced their ability to interact with copper (II) ions[40]. Since the copper homeostasis is decontrolled in PD, a novel bioassay tool was fabricated to detect mutant α-syn by cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS) methods. The proposed platform carried a fast and economical device in differentiating between α-syn and copper(II) and their structural changes in the progression of PD (see Fig. 1) [40].

While a critical electroanalytical study method was applied to appropriately detect a-Syn autoantibody, the created platform could detect PD biomarkers with acceptable sensitivity and selectivity [35]. An electrochemical and localized surface plasmon resonance (LSPR)-based biosensing device was fabricated for the precis a-Syn detection. On the other hand, a dual detection system was established for observing the morphological modifications of αS oligomers upon minor molecule

**Table 2**
Developed biosensors for detection of Parkinson's disease-related biomarkers.

| Target | Technique | Nanoparticles | Electrode | Linear Range | LOD | Ref |
|---|---|---|---|---|---|---|
| AA, DA, UA | CV | GONRs | GCE | 0.1–8.5(μ mol $^{-1}$1) | e 40.86 μA μM$^{-1}$ cm$^{-2}$ | [54] |
| DA | Photoluminescence | InP/ZnS Q.D.s | _ | 800 pM to 100 nM | 5 nM | [56] |
| Orexin A | FET | CNT, Graphene | Interdigitated | _ | _ | [69] |
| Dopamine | Electrochemically | α-Fe2O3@erGO | GCE | 12.56 μA μM–1 cm$^{-2}$ | 0.024 μM | [70] |
| a-Syn | Impedimetry | _ | Gold | 0.5 to 10 nM | 55 pM | [35] |
| AA, DA, UA. | DPV | ZnO NWAs | NWA/GF | 1 nM | 1 nM | [55] |
| a-Syn | CV | _ | Gold | _ | _ | [40] |
| a-Syn | EIS | Cysteamine-graphene oxide modified gold microelectrode | Gold | 1.2 ± 0.3 pM | 0.3 pM | [71] |
| a-Syn | CV, DPV, LSPR | Au-Nanopyramids | Au-ITO | 10–15 nm | _ | [41] |
| a-Syn | EIS | _ | Gold | 0.05 nM to 1 nM | 21 ± 4 pM | [72] |
| 8-OHG | CV, EIS, MIP | _ | Gold | 0.1 to 100 pg/ml | 0.74 pg/ml | [59] |
| 8-OHG | CV | MWCNTs | GCE | $5.63 \times 10^{-8}$–$6.08 \times 10^{-6}$ M | $1.88 \times 10^{-8}$ M | [60] |
| 8-OHG | QCM, MIP | _ | _ | 0.0116 and 0.75 M, 0.1–1 mM | 0.05 M, 0.05 μM | [73,74] |
| 8-OHG | MIP, EIS | MWCNTs | GCE | $20 \times 10^{-9}$–$3 \times 10^{-6}$ M | $3 \times 10^{-9}$ M | |
| 8-OHG | CV, DPV, XRD | Graphene oxide-ZnO | GCE | 5.0 to 5000.0 nM | 1.25 nM | [75] |
| Apo-A1 | ChA | ITO | Glass electrode | 1 pM–100 nM | 1 pM | [66] |
| Apo-E | DPV | Mesoporous silica and graphene hybrid | Graphene | $10^{-8}$ M to $10^{-14}$ M | 10 fM | [67] |
| Apo-E | Immunosensor | _ | _ | 1.0 pg/mL to 10 ng/mL | 0.42 pg/mL | [68] |
| Apo-E | Genosensor | _ | SPEs | 2 mg/L | 1.0 mA | [76] |
| Complex I | CV, | CdSe/ZnS QDs | GCE | 3.75 to 200 μg·ml$^{-1}$ | – | [51] |

**(LOD):** Limit of detection, **(XRD):** X-ray diffraction, **(DPV):** Differential pulse voltammetry, (**MIP):** Molecularly imprinted polymer, **(GONRs);** graphene oxide nanoribbons, **CV**; Cyclic voltammetry, **FET;** Field Effect Transistor, **(GCE);** glassy carbon electrode, **(α-Fe2O3@erGO);** reduced graphene oxide, **(ZnO NWAs)** ZnO nanowire arrays, **(EIS)** electrochemical impedance spectroscopy, **(a-Syn)** Alpha-synuclein, **(LSPR)** localized surface plasmon resonance, **(Au-ITO)** indium tin oxide, **(8-OHG)** 8-hydroxy-2′ -deoxyguanosine, **(MWCNTs)**; multi-walled carbon nanotubes, **(QCM);** Quartz crystal microbalance, **(Apo-A1);** Apolipoprotein-A1, (**ChA);** Chronoamperomettry, **(Fc);** Ferrocenecarboxylic acid, **(SPEs);** Graphite screen-printed electrodes.

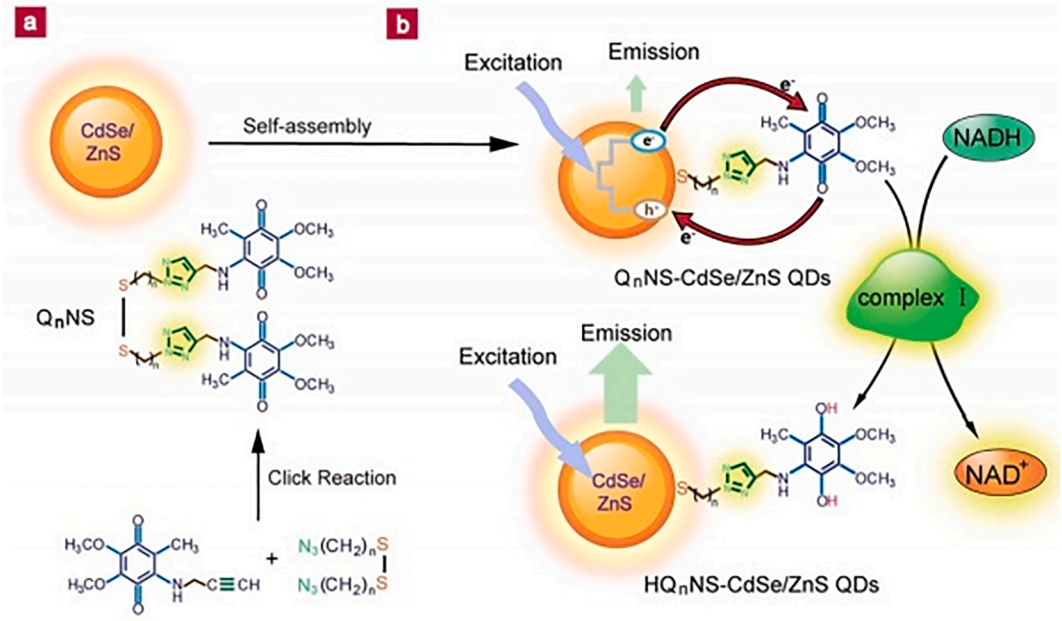


**Fig. 5.** Schematic illustration of ubiquinone-CdSe/ZnS QDs as redox fluorescence biosensor to diagnose Parkinson's disease, Theoretical imagining of **$Q_n$NS**-QDs as complex I sensor *in vitro*. In the oxidized state (**$Q_n$NS**), ubiquinone acts as a promising electron acceptor; this results in real QDs' fluorescence quenching. Following the insertion of complex I to **$Q_n$NS**-QDs solution in the presence of NADH, ubiquinone coupled electron transfer, and proton translocation from NADH, creating reduced ubiquinol (**$HQ_n$NS**) form on the surface of QDs to mimic the primary phases of the respiratory chain. Ubiquinol, when close to the QDs, yields fluorescence enhancement [51].

interactions with LSPR and electrochemistry. The alterations in the structure of a-Syn oligomers were shown as LSPR absorption band signals and oscillations in DPV peak current (see Fig. 5) [41].

### 2.2. Dopamine

Dopamine (3,4-dihydroxyphenethylamine) (DA) is one of the critical neurotransmitters of the catecholamine family that extensively circulates in the central nervous system (CNS) for communication between neurons [42,43]. Depending on location, DA concentration is below 100 nM and ranges approximately between $1.0 \times 10^{-7}$ M and $1.0 \times 10^{-3}$ M [44,45]. Several methods are used to detect dopamine, including high-performance liquid chromatography (HPLC), colorimetry, and fluorescence spectrometry [42,43]. Various biosensors have been developed

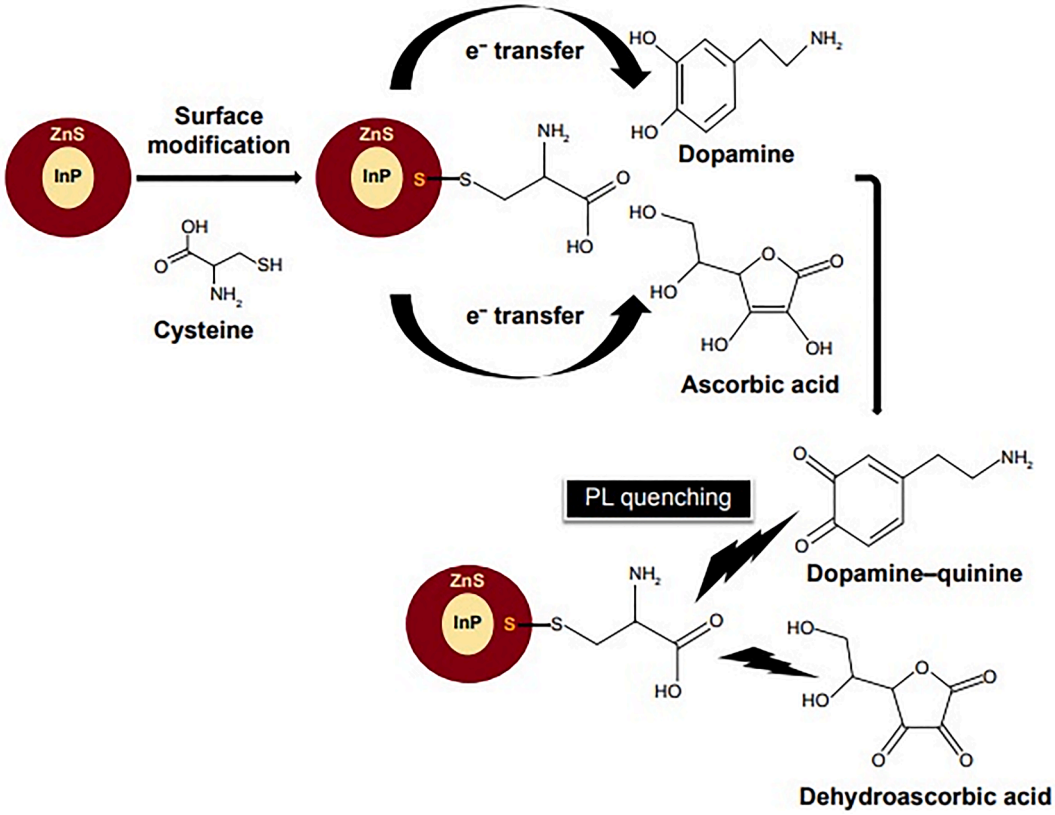


**Fig. 6.** Schematic illustration of the fluorescence quenching of cysteine-capped InP/ZnS QDs in the presence of AA and DA, PL, photoluminescence, InP/ZnS QDs, indium phosphide/zinc sulfide quantum dots; AA, ascorbic acid; DA, dopamine (3,4-dihydroxyphenethylamine) [56].

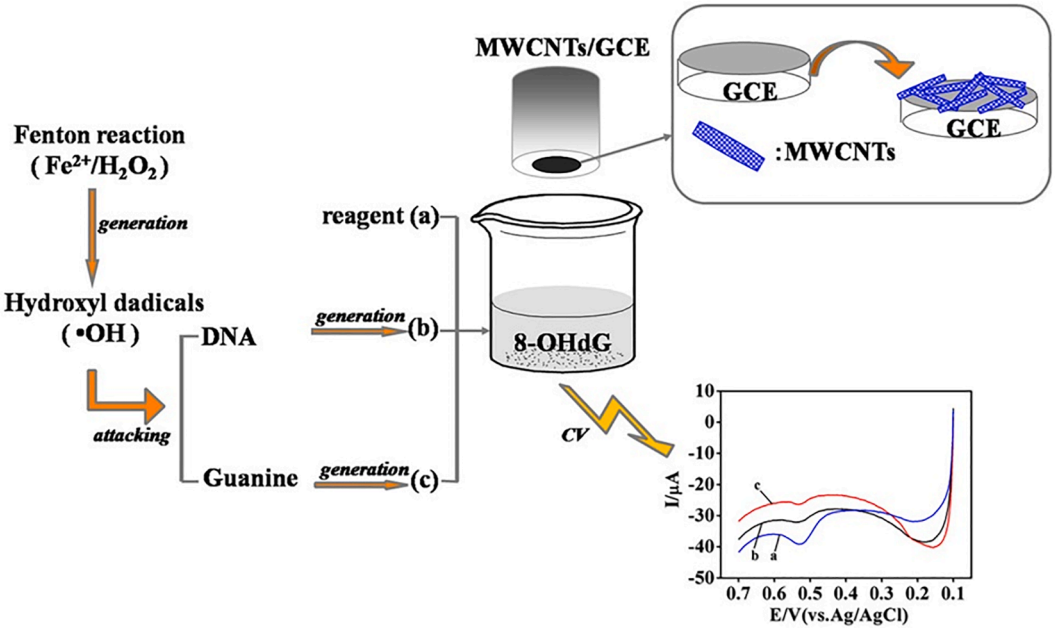


**Fig. 7.** The proposed electrochemical sensor based on the multi-walled carbon nanotubes (MWCNTs) modified glassy carbon electrode (GCE) for 8-OHdG generated from damaged DNA and guanine, respectively, as shown in the oxidation currents of 8-OHdG amplified along with the damaged DNA and guanine in specific concentrations [60].

recently to overcome the limitations of conventional methods in dopamine detection. During the novel study magnetic hematite, (α-Fe2O3) decorated with electrochemically reduced graphene oxide (α-Fe2O3@erGO) nanocomposite was fabricated detecting PD biomarkers. This method was self-assembled, outset synthesized α-Fe2O3 anchored GO to erGO (α-Fe2O3@erGO) on glassy carbon electrode (GCE) for the selective detection of PD biomarker [46].

Recent studies propose that the inhibition of the mitochondrial

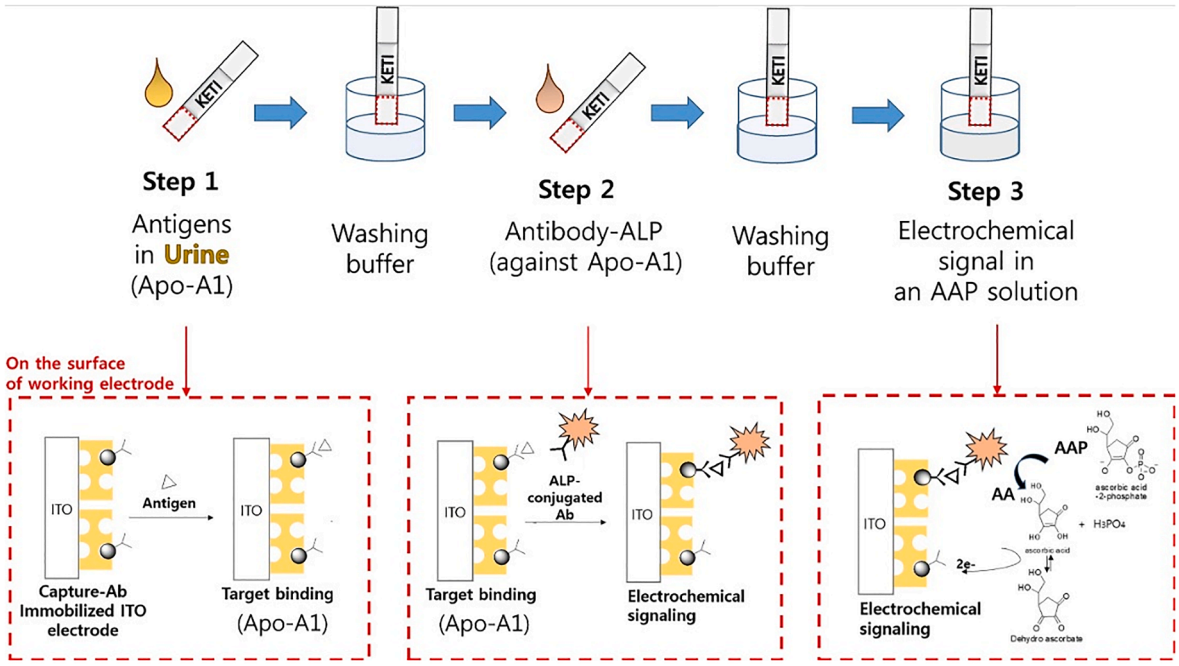


**Fig. 8.** (a) Representations of the proposed procedure for Apo-A1 detection by an ITO electrode strip. (b) Representation of direct ELISA assays on ITO electrode for identifying a biomarker in urine [66].

NADH:ubiquinone oxidoreductase (complex I) can be the primary cause of periodic PD originating from dopamine neurons' death, a main clinical symptom of PD. The association between the loss of PD progression and complex I activity may offer a path to primary PD diagnosis and monitoring [47,48]. Semiconductor quantum dots (QDs) have extensive applicability in several areas, such as clinical diagnostics, imaging, and public health, thanks to their exceptional optical properties. Wide absorption profiles, tunable fluorescence narrow emission, greater photostability, and high signal brightness are the main QD properties. Also, QDs are particularly sensitive to the presence of further charges either in the surrounding environment or on their surfaces, which can lead to a multiplicity of electronic values and optical properties [49,50] while interestingly studying QDs. Bio-conjugates for biosensing complex I, which employ 550-nm-emitting core–shell CdSe/ZnS QDs and ubiquinone-terminated disulfide ligands, were fabricated. Findings revealed that $Q_n$NS-QDs could be a bio-compatible fluorescence biosensor for the following of complex I (Fig. 7) [51].

In terms of electronic properties, graphene is generally considered the most favorable choice to substitute other materials in biosensing devices [52,53]. Among various analytes, uric acid (UA) and dopamine (DA) are the most described biomarkers of Parkinson's disease. During the investigative study, short graphene oxide nanoribbons (GONRs) were used to modify glassy carbon electrodes for UA and DA's electrochemical detection. GONRs were used successfully as an innovative platform for identifying PD biomarkers with high sensitivity and selectivity [54]. Similarly, ZnO nanowire arrays (ZnO NWAs) on 3D graphene foam (GF) were developed to detect PD biomarkers. Simultaneously, ascorbic acid (AA), (UA), and (DA) were identified selectively using the differential pulse voltammetry (DPV) method [55]. In a study, quantum dots (QDs) were applied as a sensing platform for DA recognition. The surface of the QDs was modified with l-cysteine by a coupling reaction to enhance its DA selectivity. The fluorescence of cysteine-capped indium phosphide/zinc sulfide QDs was extinguished using DA with several concentrations in the presence of ascorbic acid. This system demonstrated proper selectivity for dopamine detection with acceptable LOD (Fig. 4) [56].

### 2.3. 8-hydroxy-2′ -deoxyguanosine (8-OHdG)

Reactive oxygen species (ROS) such as $O^{-2}$ and OH can destroy biological molecules, while irreversible reactions trigger degenerative processes in the elderly. One of the key DNA damages caused by ROS produces an oxidized form of 8-hydroxyguanine (8-OHG) recognized as 8-OHdG. Several studies demonstrated that 8-OHdG serum levels increased in PD patients compared to healthy individuals; thus, 8-OHG can be used as a PD biomarker [57,58]. An innovative biosensor involved in a molecularly imprinted polymer (MIP) layer was assembled on a gold electrode through an electropolymerization monomer linkage with the template to screen urinary 8-OHdG at a low level. The developed biosensor for urinary 8-OHdG detection set up a favorable low-cost alternative to the conventional approaches, thanks to its high stability, sensitivity, selectivity, and simplicity [59].

The electrochemical sensing device was fabricated based on the multi-walled carbon nanotubes (MWCNTs) modified with glassy carbon electrodes (GCE) to detect 8-OHG. The created system showed an excellent electrochemical response to the oxidation of 8-OHdG by acceptable LOD and high sensitivity. Also, this work successfully arranged the electrochemical signal of 8-OHdG through damaged guanine DNA, suggesting a new way to associate DNA damage with the degree of the health effects (Fig. 6) [60].

A lateral flow platform was established for rapid and simple 8-OHdG detection appropriately. Despite the simple and low-cost structure, the developed system exhibited sensitivity and specificity for 8-OHdG identification [61]. Different deoxyribonucleic acid (DNA) electrochemical biosensors have been developed for sensitive identification of 8-OHdG recently with application in drug analysis and drug discovery [62].

### 2.4. Apo-lipoprotein

Apo-lipoproteins are amphipathic molecules capable of interacting with both the aqueous environment of the plasma and the lipids of the lipoprotein core[63]. They act as biochemical keys, permitting lipoprotein particles to modify lipids, access specific sites, deliver and accept molecules [63,64]. Apo-lipoprotein (apo) E is a multifunctional protein

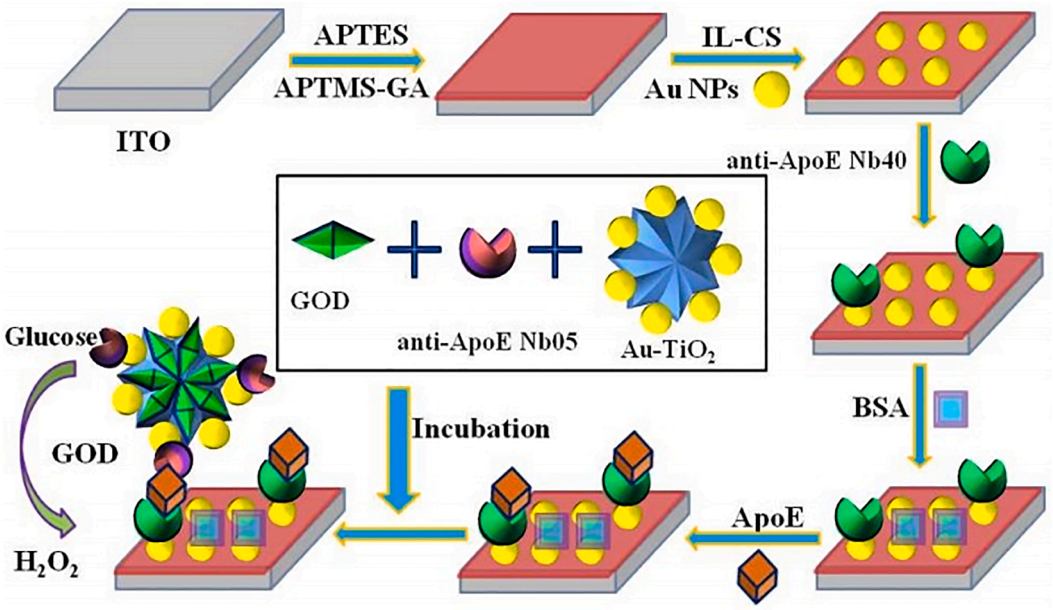


**Fig. 9.** Proposed immunosensor for detection of Apo E gene, an ApoE POCT immunosensor was fabricated using anti-ApoE Nbs. The labels of Au-TiO2@GOD @anti-ApoE Nb05 can provide a good result due to the combination of Ti-O bond and flavin adenine dinucleotide (FAD) from the GOD, representing the loading of GOD over the Au-NH2 and Ti-O interaction [68].

with fundamental significance in neurobiology, lipid metabolism, and neurodegenerative diseases [65]. Additionally, apo-lipoprotein E is a key protein in plasma with an imperative role in the lipids' metabolism and transport in serum and the central nervous system (CNS). A novel and simple electrochemical immunosensor was developed to recognize Apo-lipoprotein A1 (Apo-A1) as an essential biomarker in urine. The developed system sensitively identified Apo-A1 as a biomarker in both urine and PBS with high repeatability using the chronocoulometry technique (Fig. 7) [66].

For accurate, sensitive, and selective identification of mutated Apo-lipoprotein E gene related to Alzheimer's disease, a novel label-free ratiometric electrochemical nano-biosensor was fabricated. Low-cost and straightforward structure, fast performance, and sensitivity were essential features of the developed platform and promised an ideal alternative to the conventional methods [67]. A similar immunosensor was established for Apo E detection (Fig. 8) [68].

## 3. Conclusion

Parkinson's disease (PD) is the second most common neurodegenerative disease. Therefore, the correct diagnosis of PD is important for prognostic and therapeutic reasons and is essential for clinical research. This study aimed to reveal the biosensor technology's significances as a simple, cost-effective, reliable approach to identifying PD-associated biomarkers. Surprisingly, just a few systems have been developed thus far for PD despite the increasing development of biosensors in various diagnostic fields. The most critical considerations in PD biosensors' development include: 1- Parkinson's specific biomarkers such as alpha-synuclein should be given more attention. 2- Using appropriate functional nanomaterials as well as graphite and gold nanoparticles in biosensors assembly, significantly increases the sensitivity and diagnostic quality. 3- The key features of biosensors include simple, inexpensive easy fabrication and functionalization, well-defined and controllable structures at the nanometric scale, biocompatibility. 4- Several studies demonstrated, gene-based biosensors are highly specific and sensitive; thus, genosensor development can be considered as the best alternative for old and routine methods (see Fig. 9).

## Declaration of Competing Interest

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

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