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Current Advances in Electrochemical Biosensors and Nanobiosensors

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ABSTRACT

Electrochemical biosensors have wider interest in the last decades than other analytical techniques such as chromatography, spectrophotometry, fluorescence, migration techniques and flow systems. Since they provide practicality, sensitivity, and fast response, these systems can be integrated with labs-on-chips to obtain excellent point of care analytical platforms. They are excellent devices for wide range of analytes such as drugs, proteins, markers, bacteria, and viruses etc. due to their unique features. Electrochemical methods are also successful at molecular recognition, user friendliness, sensitive responses, requirement of small volume reactive of reagents, low cost, and applicability to point of care tests. DNA, enzyme and immunosensor based biosensors are widely used as well. According to recent studies of electrochemical biosensors, nanomaterials and polymers have been used to increase the performance of biosensors. In this review, the recent studies of electrochemical biosensors have been presented with their applications at various fields.

KEYWORDS

Biosensors; DNA; electrochemistry; enzyme; immunosensor

Introduction

Biosensor are of increasing interest in the fields of medicine, industry, environment, process control, biological samples and many other fields. Hence, a lot of studies have been devoted to fabrication of selective, sensitive, versatile nanomachines for targeting analytes by electrochemical, mass sensitive and optical methods. In these methods, electrochemical studies have broad application, especially amperometric, impedimetric, potentiometric and voltammetric techniques.[1,2] Bakker and coworkers presented chronopotentiometry and coulometry with their methodologies.[3–8] Ion selective sensors are frequently by many researchers due to their easy usage for point of care diagnostics and portability in environmental fields.[9–11] Due to developed technology; wearable and tattoo body sensors (Figure 1) have been designed for biological detections.[12,13]

Electrochemical biosensors are mostly used due to their low cost, stability, easy application, low sample requirement and low detection limits[14–18] which making them more preferable for commercial aspects.[19] The first glucose biosensor was reported in 1962 by Clark and Lyon. In 1975, this types of biosensor was commercialized under the trade name "Model 23 A YSI analyzer".[20] In the following two years, other achievements such as first microbial biosensor and beside artificial pancreas were performed. After ten years, first plasmon resonance immunosensor were also made. In 1987, blood glucose biosensor was introduced by MediSense ExacTech Inc.[2,21]

Especially, nanomaterials, conducting polymers, biopolymers, composites have been applied in the fabrication of electrochemical biosensors.[19–26] Electrochemical biosensors involve an analyte, receptor, transducer and recording system.[27–36] For example, acetylcholinesterase can be receptors which biorecognition element for analyte. This enzymes can produce electrons with known signals. In other side, transducer is used to transfer the signal into the measuring device for data recording usually by a computer. DNA biosensors are frequently used for disease diagnosis, biomarker detection, drug-DNA interaction and DNA hybridization.[37–42] DNA biosensors are preferred also for gene detection due to their sensitivity, low cost and simplicity. Immunosensor based biosensors are preferred for the detection of the protein biomarkers, lipoproteins, bacteria, food pathogens and viruses. Electrochemical immunosensors have great advantages such as accuracy, sensitivity, molecular recognition capability and no need for separation or pretreatment before analysis. Electrochemical impedance spectroscopy is the most used method for electrochemical immunosensor investigations. The change in resistance, current, capacitance is evaluated analyte and receptor interactions. Thanks to the improvement of existing detection technologies and the development of nano- and bio-materials, innovative functional sensor materials, and precise miniature sensors, better opportunities are emerging for the construction of new generation biosensors with much improved performances are emerging. In this regard, electrochemical sensors may specific to a target compound with

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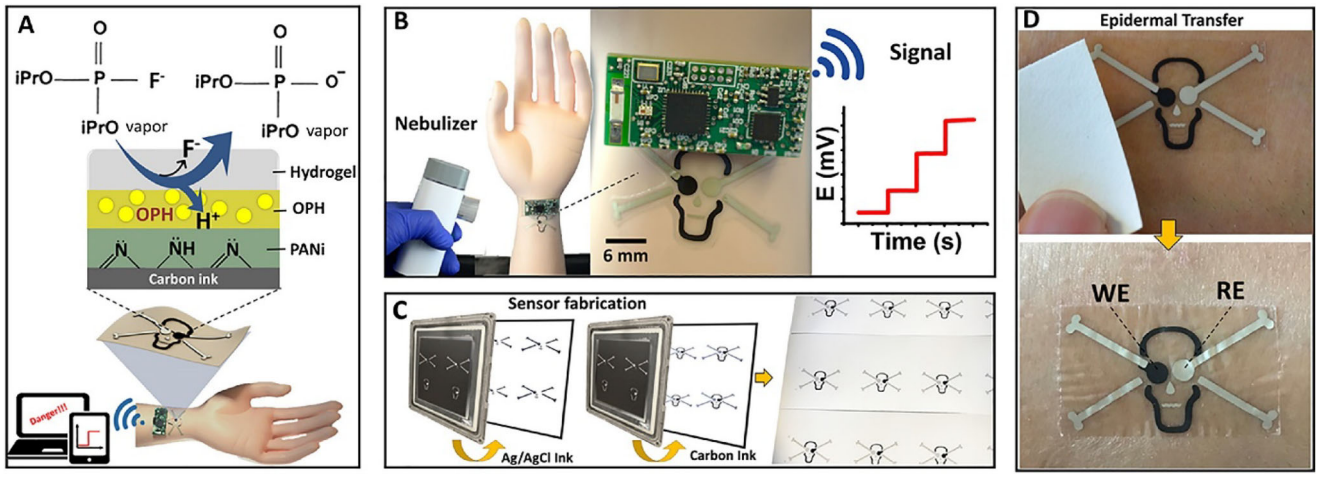


Figure 1. Tattoo based biosensor for detection of nerve biomarkers; A) Fabrication of polymer based tattoo biosensor on carbon based substrate and observing data by wireless B) Integration of biosensor on mannequin via nebulizer C) Printing of sensor on paper based tattoo approach samples D) Application of tattoo based sensor on skin. Reprinted with permission from.[12]

giving a linear output, low power requirements and good resolution. It has excellent repeatability and accuracy, less expensive than most other techniques. Their effects are most clearly demonstrated in the widespread use of electrochemical sensors seen in daily life, where they continue to meet the growing need for fast, simple and economical detection methods for a large number of drug active compounds. When developing electrochemical sensors, it should be noted that they have one of two properties: they have increased specificity or they can perform simultaneous/multiplex determinations.

However, it has narrow or limited application area in the marketing. They have short or limited shelf life between six months and one year. Some electrochemical sensors are subject to interference from other compounds. It is important to know which compounds may cause tis interference with the proposed sensor. In both of these branches, the ability to operate in complex biological matrix will remain critical, forcing researchers to solve problems of biocompatibility and stability. Therefore, features to consider when developing and commercializing biological sensors primarily include: must be cheap, small, precise, reproducible, selective/specific, suitable for multiple analyte detection and stable. Few, if any, sensors exhibit optimum properties for all features. When developing electrochemical biosensors, some features may be prioritized over others depending on the final application and target compound.

It is thus timely to summarize recent progress in this diverse field and to discuss its future prospects for development. After introducing the types of electrochemical biosensors, this review will describe the most frequently used electrochemical biosensors and their applications on drugs, DNA, enzymes and other biomolecules.

Electrochemical DNA biosensor: drug-DNA interaction

The cellular DNA is the major target of drugs, especially anticancer, antiviral and antibacterial agents. In general, DNA-interacting agents may be classified as covalent and noncovalent. The covalently binding is irreversible and causes cell death. The non-covalent binding is reversible, can change DNA conformation and potentially lead to DNA strand breaks. Non covalent binding includes electrostatic interaction, intercalation and minor/major DNA groove binding interaction. The studies on interaction between drugs and DNA is necessary to explain the interaction mechanism in addition to design DNA targeted agents.[43–45]

Electrochemical investigations on DNA are important to clarify many biological mechanisms. Electrochemical studies demonstrated that DNA bases (purines and pyrimidines) can be electrochemically oxidized on carbon electrodes.[46] The guanine and adenine, give responses at less positive potentials than the cytosine and thymine. The electrochemical DNA biosensors with a bio-component connected to a physical transducer are sensitive to the physicochemical interaction between the bio-component and the analyte of interest.[47] They offer good model to simulate the DNA interactions with cell membranes, carcinogenic agents and drugs. In recent years, the electrochemical biosensors display obvious superiorities in detecting DNA damage and elucidate the mechanisms of interaction between DNA and drugs. The drug-DNA interaction may be investigated using three different strategies, namely DNA modified electrode, drug-modified electrode, and interaction in incubated solution. To understand the drug–DNA interactions, the pre- and post-voltammetric peak current and potential of either the drug or DNA bases can be monitored.[44,48] Also, the irreversible DNA damages could be observed by the occurrence of peak of 8-oxoguanine. The 8-oxoguanine is the biomarker of oxidative DNA damage.

Many research articles on drug-DNA interactions have been published using electrochemical methods. Ilkhani and coworkers investigated the interaction between doxorubicin and DNA (breast cancer gene BRCA1 sequence) at gold electrode modified with a reduced graphene oxide (rGO) that decorated with plasmonic gold coated magnetic nanoparticles (AuDE/CYS/rGO/Fe_2Ni@Au).[49] They presented that the AuDE/CYS/rGO/Fe_2Ni@Au/dsDNA platform can

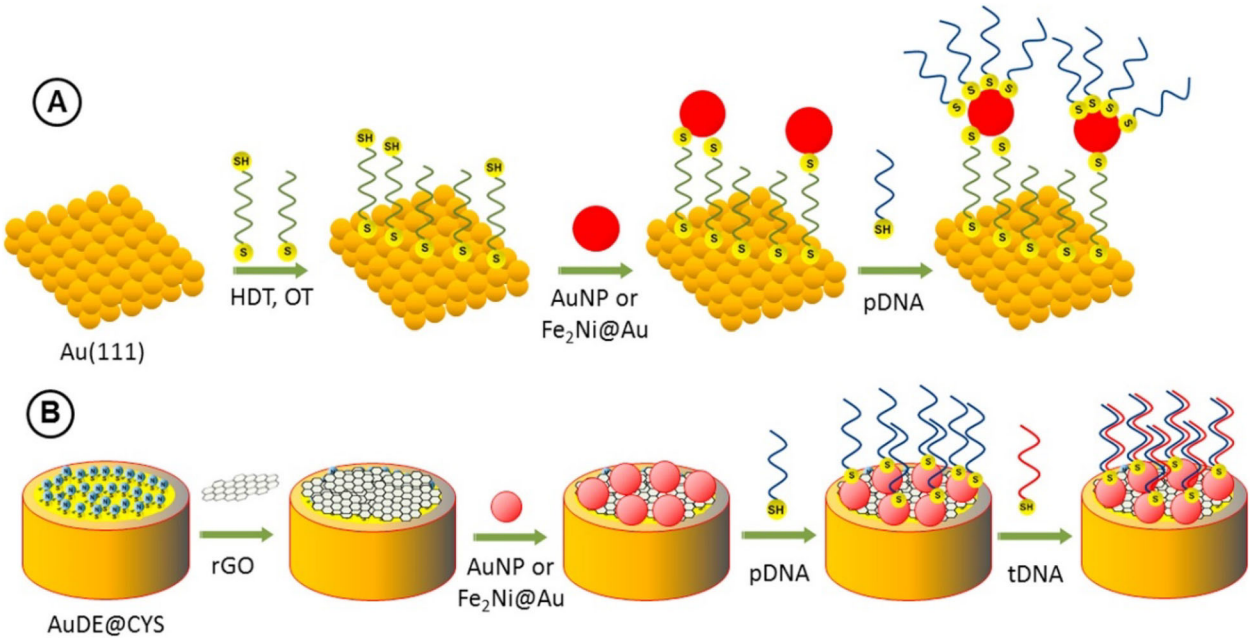


Figure 2. A) Design of SERS (Au 111)/electrochemical biosensor for investigation of drug DNA interaction B) Immobilization of nanobiomaterials on gold disk electrode. Reprinted with permission from.[24]

be used for monitoring the DNA modification or damage after interaction with anticancer drugs (Figure 2). The SERS results have confirmed that the doxorubicin intercalated into the DNA. The electrochemical measurements have showed that the linearity in the concentration range from 0.003 to 5 $mgmL^{-1}$ fitted with semi-logarithmic calibration curve. The limit of detection was 0.008 $mgmL^{-1}$.

Heydari and coworkers studied the interaction between tamoxifen and i-motif structure of human telomeric DNA sequences.[50] The electrochemical sensor was fabricated based on SiO_2 nanoparticles modified carbon paste electrode. The interaction was studied by cyclic voltammetry (CV) and square wave voltammetry (SWV). Shervedani and coworkers examined the interaction between methotrexate and biological species including calf thymus DNA, mouse 4T1 breast tumor, and Human foreskin fibroblast cells using surface analysis techniques and electrochemical techniques.[51] Methotrexate was immobilized onto the graphene surface by three methods including organic activators, electrografting, and noncovalent bonding. The results show that the maximum amount of the immobilized methotrexate was obtained with electrografting method. Untiveros and coworkers developed a new electrochemical biosensor for detection of DNA damage caused by intercalated anti-cancer compound (7ESTAC01).[52] The interaction between this compound and DNA was investigated on gold electrode surface using Differential pulse voltammetry (DPV).[52] In the presence of 7ESTAC01, the peak currents of guanine and adenine were increased and led to the formation of 8-oxoguanine peak.

Other current research studies within recent years that concerned on DNA-drug interaction by electrochemically are summarized in the Table 1.

Enzyme based electrochemical biosensors

Generally, biosensors are classified based on the biological constituent used, such as enzymes, nucleic acids, antibodies, or cells, or by the sort of transducer. Biomimetic sensor area is an emerging class of sensor technology, which offers several advantages compare to traditional sensor area. Biomimetic sensor include mimicry of biological function, morphology, behavior, and manufacturing but not all of them function according to the biological principle being mimicked.[77] Enzyme-based electrochemical sensors are inexpensive and rapid compared to other classical methods, such as chromatographic methods.[78] The electrochemical enzyme based biosensor, which contains the enzyme as a bio-recognition element, is followed as an interesting research topic in the field of health and environment. A biosensor is a tool closely connected to a transducer or comprising an integrated biological sensing element.[79] An enzyme biosensor consists of two main components: a bioreceptor (enzyme) and a transducer to produce a signal proportional to the target compound amount.[77,78] The enzyme selectively reacts with the target analyte and generates an electrical signal based on the analyte concentration. The creation of the biosensor exactly began with the efforts of Leland C. Clark, Jr. to measure oxygen in biological fluids. The concept of an enzyme-based tool was introduced by Clark in 1962 and was achieved as a commercial clinical analyzer in 1975.[80] This part will focus on significant advances enzyme based biosensor, most of which have occurred in the last 5 years. Glucose, lactate, urea and glutamate/glutamine are commonly used sensors for practical and commercial use (Supplementary file). The enzyme immobilization procedure is a crucial step in the

Table 1. Some selected studies on DNA based biosensors.

Drug	Method	Electrode	Medium	Binding constant	Linearity range	*LOD/LOQ*	Suggested interaction mechanism	Ref.
Mitomycin C	DPV	CTS/CNT/PGE	pH 4.8 ABS	NS	NS	6.85 μgmL^{-1}	Cross-linking	[53]
Topotecan	DPV, EIS	SWCNT/PGE	pH 4.8 ABS	NS	NS	0.37 μgmL^{-1}	Intercalation	[54]
Aripiprazole	CV, DPV	GCE	pH 4.7 ABS	3×10^5 M^{-1}	NS	NS	NS	[55]
Taxol	DPV	PGE	pH 4.8 ABS	NS	2.0×10^{-7} -1.0×10^{-5} M	8.0×10^{-8} M	Intercalation	[56]
Furazolidone	DPV	TiO_2-rGO-CPE	pH 4.8 ABS	NS	1.0–150.0 $pmolL^{-1}$	0.55 $pmolL^{-1}$ (G) 0.43 $pmolL^{-1}$ (A)	NS	[57]
5-fluorouracil	DPV	p(BCP)/GCE	pH 4.8 ABS	1.4×10^3 M^{-1}	1.0–50 mgL^{-1}	0.31 mgL^{-1}	Intercalation	[58]
Atropin	DPV, EIS	PDDA–TiO2NPs–MWCNTs/PGE	pH 4.8 ABS	NS	0.6 – 30.0 $\mu molL^{-1}$	30.0 $nmolL^{-1}$	Intercalation	[59]
Morphine	DPV	Au/MB	pH 5.0 PBS	NS	0.05–500 $\mu molL^{-1}$	0.01 $\mu mol\ L^{-1}$	Intercalation and electrostatic	[60]
Mercaptopurine	DPV, CV	PP/ MWCNTs / PGE	pH 4.8 ABS	NS	0.2 – 100 $\mu molL^{-1}$	0.08 $\mu molL^{-1}$	NS	[61]
Riboflavin	CV, SWV	Fe_2O_3/MWCNT-AuNPs/GCE	pH 4.8 ABS	NS	0.3 µM-60 nM	6 nM	NS	[62]
Gemcitabine	DPV	P(PDCA) /GCE	pH 4.8 ABS	4.6×10^4 M^{-1}	1–30 mgL^{-1}	0.276 mgL^{-1}	Groove binding	[63]
Ganciclovir	SWV, CV	Fe_3O_4 / MWCNTs / GCE	pH 7.4 PBS	2.0×10^4 M^{-1}	80–53.000 nM	20 nM	Intercalation	[64]
Vitamin B1	DPV, CV	MWCNTPE	pH 6.3 ABS	5.097 M^{-1}	NS	NS	Electrostatic	[65]
Lomustine	CV,SWV	HMDE	pH 7.4 PBS	1.6×10^5 M^{-1}	2.39– 10.95 μM	4.95×10^{-8} M	Intercalation	[66]
6-Tiyoguanine	CV, DPV, EIS	SWCNT-PGEs	pH 7.4 PBS	NS	NS	0.25µM	Intercalation	[67]
Tamoksifen	DPV	GPE	pH 4.9 ABS	NS	8.0×10^{-7} -8.5×10^{-5} M	1.0×10^{-7}	NS	[68]
Cisplatin	AdSV, DPV	ERGO/GCE	pH 4.7 ABS	NS	10-100µM (G) 1-100µM (A)	0.3µM (G) 0.2µM (A)	Covalently-linked	[69]
Daunorubicin	DPV	Ag-4-ATP-MWCNT	pH 7.0 PBS	NS	0.1×10^{-8} -1.0×10^{-5} M	3.0×10^{-10} M	Intercalation	[70]
Valrubicin	CV	MWCNT/Pt	pH 7.4 PBS	1.75×10^3 M^{-1}	NS	NS	Electrostatic and intercalation	[71]
Miltefosine	DPV	GCE	pH 4.5 ABS	NS	NS	NS	Complex	[48]
Tenofovir	CV, SWV	BDDE (in solution)	pH 7.4 PBS	6.8×10^6	NS	NS	Intercalation	[72]
Theophylline	CV, SWV	GCE	pH 7.4 PBS	NS	NS	NS	H-bonds	[42]
Didanosine	DPV	PPy/ rGO/PGE	pH 4.8 ABS	NS	0.02–50.0 µM	8.0 nM	NS	[73]
Daunorubicin	DPV	CTS-PGEs	pH 4.8 ABS	NS	2.50–10 μgmL^{-1}	0.60 μM	intercalation	[74]
Quinacrine	DPV, CV	Carbon dots/GCE	pH 4.5 ABS	2.0×10^4 M^{-1}	NS	NS	intercalation	[75]
Prednisone	DPV	GCE/AgNPs/P(GBHA)	pH 4.8 ABS	2.8×10^5 M^{-1}	1.0–50.0 μgmL^{-1}	0.3 μgmL^{-1} 0.25 μgmL^{-1}	intercalation	[76]

construction of enzyme based on electrochemical sensor.[79–81] Enzymes can be immobilized to the surface of a transducer by different immobilization methods such as physical adsorption, covalent attachment, incarceration, encapsulation and covalent crosslinking.[82] Studies on the application of electrochemical enzymatic biosensors with analytical applications in the literature are summarized in Table 2.

Nesakumar and coworkers fabricated a biosensor based on PtE/ZnO/AChE/Chitosan for the detection of carbosulfan in rice sample using cyclic voltammetry.[113] The ZnO sample was characterized using FE-SEM and X-ray diffraction. Effect of incubation time on AChE inhibition using electrode in 0.1 M, pH 7.4 PBS containing 0.08 mM ATChCl and 5 nM carbosulfan performed at a scan rate of 0.11 V s^{-1} was investigated. 20 min was selected as the working incubation time. In the range of 5–30 nM carbosulfan was detected with LOD of 0.24 nM.

Zhang and coworkers suggested an electrochemical biosensor for the detection of organophosphorus pesticides.[114] The AChE/OMC-CS/ATO-CTS/SPCE biosensor was examined with cyclic voltammetry. The DPV responses of methamidophos and chlorpyrifos were examined with LOD of 1 mgL^{-1} and 0.05 mgL^{-1}, respectively. The recovery studies were performed by adding different amounts of pesticides into vegetables samples. In another work, Wei and Wang developed a novel AChE/[BSmim]HSO^{4-}AuNPs-porous carbon/BDD sensor for determination of dichlorvos.[115] The SEM and TEM images were used to examine the structure of the prepared materials. The electrode surface modification was confirmed with CV and electrochemical impedance spectroscopy (EIS). LOD of dichlorvos was achieved with a detection limit of 0.3 pM.

Zhang and coworkers suggested a biosensor based on GCE-MWCNT–$(PEI/DNA)_2$/OPH/AChE.[116] Paraoxon responses were examined on this sensor via CV with LOD 0.5 μM. They reported production, optimization and characterization of biosensor using CV, EIS, surface plasmon resonance technique (SPR), and UV–vis spectrophotometry (Figure 3).

Immunosensor based electrochemical biosensors

In recent years immunosensors have drawn an attention in a range of applications from clinical examination to environmental sensing. Immunosensors, one of the immunoassay techniques, have all the basic performance characteristics of immunoassays. They are a biosensors using immunoactive substances as biospecific sensitive elements and are based on the complex formation of the antibody linked with the appropriate antigen. Therefore, the antibody-antigen reaction is highly selective. This recognition reaction is defined by the transducer device with highly selective, sensitive and specific properties. The immunosensor is based on three separate parts: the biological recognition area, the physicochemical transducer and the electrical instruments. Antibodies are capable of recognizing antigen over a wide range, from low molecular structures (haptens) to large molecule structures (bacteria). The specific regions of the antigens, called as the epitope, only cause this immune response. The epitope also bridges over for the binding site for the appropriate antibody. The interaction between the antibody and the antigen are made with different binding bond - hydrogen bonds, Van der Waals, hydrophobic and electrostatic interactions. Electrochemical immunosensors are measured with different kind of electrical signals in redox probe. Electrochemical measurements require a conductive platform as an electrode produced with different kinds of nanomaterials. Label-free electrochemical immunosensor is described as cheap, simple, portable and disposable devices without "label." It has become one of the alternative quantitative method for early detection of biomolecules.

In Ruecha et al. study, label-free immunosensors were constructed for high sensitive determination of Human interferon gamma (IFN-γ) (Figure 4).[118] The INF-sensing platform was obtained with graphene (G) linked screen-printed paper electrode modified by electrodeposited polyaniline (PANI). The label free PANI-G platform has attracted attention because of affordable, low-volume consumption, disposability, and rapid analysis. The sensors exhibited excellent performance at IFN-γ concentrations ranging from 5 to 1000 $pgmL^{-1}$ with LOD 3.4 $pgmL^{-1}$. In decade, the collaboration in nanotechnology and bioelectronics has paved the new valuable way to scale down and design sensitive immunosensor modified with different nanomaterials. For that, Chen and coworkers fabricated a label-free electrochemical immunosensor modified with AuNPs for highly sensitive and selective detection of the OMP31.[119] The electrode surface was then formed by the covalent binding of GSH and HA onto gold electrode surface. GSH was effectively conjugated onto HA by EDC/NHS. EDC/NHS reaction are often selected as an easy and effective way to activated the carboxy group. The developed OMP31-immunosensor based on HA/GSH/AuNps/GCE demonstrated high sensitivity of 0.50 $fgmL^{-1}$ (S/N = 3) and linearity in the range from 2.08 $fgmL^{-1}$ to 1.04 $pgmL^{-1}$.

Enzyme, such as HRP, Glucose oxygenase (GOX), peroxidase, alkaline phosphatase (AP), electrochemical active molecules such as ferrocene or fluorescein, fluorescence markers such as rhodamine, phosphorescence porphyrin dyes can be commonly employed in immunosensors for monitoring electrochemical signal through their biocatalytic reaction. The immobilization method employed to link the bioelement to the type of transducer is very important for the performance of the biosensor. In Guerrero and coworkers studies, a electrochemical immunosensor was proposed for the novel detection of TGF-β1 based on SPAuE modified with grafted p-aminobezoic acid.[120] The sandwich-type immunoassay was fabricated by simple, disposable and affordable screen-printing technique. The AP-Strept-Biotin-anti-TGF-TGF-β 1-anti-TGF-SPAuE immunosensor was synthesized to determine the TGF-β 1. The detection limit showed that the novel immunosensor had good performance in the concentration of TSH from 0.05 and 3.0 $ngmL^{-1}$ and LOD 10 $pgmL^{-1}$. By G. Martinez-Garcia and coworkers, a novel

Table 2. Some selected studies on enzyme based biosensors.

Compound	Electrode Type	Method	Enzyme	Sensitivity	Linear Range	LOD	Application	Ref.
Atrazine	MWCNTs/PVA-SPG/ Tyr/SPE	CV	Tyrosinase	NS	0.5–20.0 ppm	0.3 ppm	Water sample	[83]
Capsaicin	PAL/Nafion/MWCNTs/ Pt-E	DPV	Phenylalanine ammonia-lyase enzyme	NS	NS	0.1863 ppm	Real sample	[84]
Carbaryl	GCE/rGO/AChE	DPV	Acetylcholinesterase	NS	NS	1.9 nM	Fruit sample	[85]
Catechol	Lac/GA/PANI/ GCE	CV	Laccase	706.7 mA.L.moL^{-1}	3.2×10^{-6} – 1.96×10^{-5} M	2.07×10^{-6} M	Buffer	[86]
Catechol	Lac/ZnS:Ni/ZnS/GCE	CV	Laccase	NS	0.1-100 μM	35 nM	Water sample	[87]
Catechol	Lac/SPAuE	CA	Laccase	3.93 μA μM^{-1} cm^{-2}	0.02-2.4 mM	1.2 μM	Wastewater sample	[88]
Catechol	PEDOT-rGO-Fe2O3-PPO	DPV	Tyrosinase	NS	4×10^{-8} –6.20×10^{-5} M	7×10^{-9} M	Buffer	[89]
Catechol	GrE/GNRs/AgNPs/PPO	DPV	PPO	NS	2–2300 µM	0.03 µM	Real sample	[90]
Catechol	SPEs/MWCNTs/ AuNWs/Tyr	CA	Tyrosinase	NS	0.5- 42 μM	0.027 μM	Buffer	[91]
Cholesterol	Ag/GO&CHER&CHOD/Au NPs/SPE	LSV	CHOD CHER	0.084 μAcm^{-2} ppm	0.01 – 5000 ppm	0.001 ppm	Buffer	[92]
Cholesterol	ChEt-ChOx / ZnO-CuO /ITO/glass bioelectrode	CV	ChOx ChEt	760 mAcm^{-2}µM	0.5 – 12 µM	NS	Human serum samples	[93]
Cholesterol	Ag/CHER&CHOD/Au NPs/SPE	ASV	CHOD CHER	NS	5–5000 μgmL^{-1}	3.0 μg/mL	Buffer	[94]
Cholesterol	GCE/PPI/QDs/ChOx	SWV	ChOx	111.16 µAmM^{-1} cm^{-2}	0.1-10 µM	0.075 µM	Buffer	[95]
Chlorpyrifos	AChE/OMC-CS/ATO-CTS/SPCE	DPV	Acetylcholinesterase	NS	0.01–105 µgL^{-1}	0.01 µgL^{-1}	Actual samples	[96]
D-alanine	DAAO/PTCA/ MWCNTs/GCE	CV	DAAO	NS	1.0×10^{-8} – 1.0×10^{-3} M	3.3×10^{-9} M	Real sample	[97]
Dopamine	SPE/rGO-CDBA-Lac	DPV	Laccase	0.1041 µAµM^{-1} 1487.1 µA/mM/cm^2	0.1–70 µM	0.03 µM	Human urine samples	[98]
Dopamine	Tyrosinase/NiO/ ITO electrode	CV	Tyrosinase	0.06 µAµM^{-1}	2-100 µM	1.0375 µM	Real sample	[99]
Glucose	Pd–Au NPs/GOx/C-modified glassy carbon electrode	CV	GOx	7.97 mA(mM cm^2)$^{-1}$	NS	0.0014 mM	Human blood samples	[100]
Glucose	Nafion/GOx/AuNPs/ ZnONRs/ITO	CV	GOx	14.53 2.54	0.05–1.0 mM 0.1–20 mM	0.18 mM	Buffer Buffer	[101]
Glucose	CH-GOx/PPy-Nf-fMWCNTs/GCE	CV	GOx	2860.3 µAcm^{-2} mM^{-1}	0.01–4.7 mM	5µM	Real serum samples	[102]
Glucose	GOx/AuNPs/BSA/Fe3O4	CA	GOx	115.3 μAmM^{-1}cm^{-2}	0.25–7.0 mM	3.54 µM	Buffer	[103]
Glycerol	GKNPs/GPONPs/ GrONPs/PGE	CV	GK GPO	121.45 μAmM^{-1}cm^{-2}	0.001–60mM	0.002 μM	Buffer	[104]
Methamidophos	AChE/OMC-CS/ATO-CTS/SPCE	DPV	Acetylcholinesterase	NS	NS	1 µgL^{-1}	Actual samples	[96]
Phenol	Tyr/CTAB-NCC/QDs/SPCE	DPV	Tyrosinase	0.078 μAμM^{-1}	5–40 μM	0.082 μM	Real samples	[105]
Phenol	HRP/HRP/GCE	DPV	HRP	NS	3.0–100.0 μM	2.19 μM	Human serum sample	[106]
Tetracycline	PEI/TetX2/NPGCE	CV	TetX2 monooxygenase	37.56 μAμM $^{-1}$ cm^{-2}	0.5–5 μM	18 nM	Real food sample	[107]
Tyramine	Poly (MPAA)/CGL	DPV	Tyrosinase	NS	10.0 – 60.0 μM	3.16 μM	Wine sample	[108]
Urea	Poly(propylene-co-imidazole)/gold nanoparticles/ urease/AuE	DPV	Glutamate Dehydrogenase	NS	0.1- 30 mM	36 µM	Wastewater sample	[109]
Uric acid	UOx/Au-rGO/ITO	DPV	UOx	86.62 ± 0.19 μAmM^{-1}	50–800 μM	7.32 ± 0.21 μM	Human serum samples	[110]
17α-ethynylestradiol	GCE/ SWCNT/C-dot/Lac	DPV	Laccase	NS	0.05–7 µM	4.0 nM	Real samples	[111]
2,4-dichlorophenoxy acetic acid	MWCNTs/PVA-SPG/ AIP/SPE	CV	AIP	NS	2.1–110 ppb	1 ppb	Water samples	[112]

Table 3. Some selected studies on immunosensor based biosensors.

Analyte	Method	Substrate	Linear range	*LOD/LOQ*	Application	Ref.
PSA Myo	EIS	Nanocomposite/ MIP/ DTSP/SPAuE	0.01–100 $ngmL^{-1}$ 1–20000 $ngmL^{-1}$	5.4 $pgmL^{-1}$ (PSA) 0.83 $ngmL^{-1}$ (Myo)	Human serum Urine samples	[122]
CysC	LSV	S-AP/biotinAb_2/CysC/ cAb_1/SPCEs	10 – 100 $ngmL^{-1}$	6.0 $ngmL^{-1}$	Biological fluids	[123]
Myo	DPV	AuNPs@rGO/SPCE	1-1400 $ngmL^{-1}$	~0.67 $ngmL^{-1}$	Spiked serum samples	[124]
GFAP	EIS	PEI/SPCE	1 $pgmL^{-1}$ – 100 $ngmL^{-1}$	0.1 $pgmL^{-1}$	Saline, artificial cerebrospinal fluid, and human blood serum	[125]
IL-1β TNF-α	CA	HOOC-Phe-DWCNTs/SPCEs	0.5-100 $pgmL^{-1}$ (IL) 1 – 200 $pgmL^{-1}$ (TNF)	0.38 $pgmL^{-1}$ (IL) 0.85 $pgmL^{-1}$ (TNF)	Serum Saliva samples	[126]
TNF-α	DPV	SB–EA–anti-TNF- α /DTSP/Au electrode	500 $pgmL^{-1}$ –100 $ngmL^{-1}$	60 $pgmL^{-1}$	Real patient samples	[127]
CRP	ASV	BC/graphite SPEs	0.2-100 $ngmL^{-1}$	0.05 $ngmL^{-1}$	Human serum samples	[128]
AXL	CA	HRP-Strept-Biotin-anti-AXL- AXL-anti-AXL-pPPA/SPCE	5 – 700 $ngmL^{-1}$	337 $pgmL^{-1}$	Human serum sample	[129]
MUC1	DPV	GO-COOH-SPCE	0.1- 2 UmL^{-1}	0.04 UmL^{-1}	Human serum samples.	[130]
cTnT	DPV	Glycine/anti-cTnT/ graphene/SPE	0.01 – 1 ng mL^{-1}	0.005 $ngmL^{-1}$	Serum samples	[131]
AXL	DPV	anti-AXL/fGQDs/SPCEs	25 – 250 $pgmL^{-1}$	0.5 $pgmL^{-1}$	Human serum sample	[132]
BNP	CA	AuNPs-S-Phe-SPCE	0.014 – 15 $ngmL^{-1}$	4 $pgmL^{-1}$	Human serum samples	[133]
HBsAg	DPV	hemin/G-quadruplex/ Fe_3O_4-AuNPs/GCE or H-amino-rGO-AuNps/GCE	0. 1–1000 $ngmL^{-1}$	10 $fgmL^{-1}$	Spiked human serum samples	[134]
NSE	DPV	AuNps/MSNPs/GCE	0.1-2000 $ngmL^{-1}$	0.05 $ngmL^{-1}$	Serum specimens	[135]
CK	EIS	Au(MPA)/APTES/ITO	10 $ngmL^{-1}$-0.5 μgmL^{-1}	0.0037 $ngmL^{-1}$	Serum sample	[136]
CA 15-3 HER2-ECD	LSV	Abs/bi-SPCE- AuNPs	5.0 UmL^{-1} (CA 15-3) 2.9 $ngmL^{-1}$ (HER2-ECD)	CA 15-3: 5.0 UmL^{-1}; HER2-ECD: 2.9 $ngmL^{-1}$	Buffer	[137]
cTnT	SWV	I-Py/CTS/AuNps/GCE	0.20-1.00 $ngmL^{-1}$	0.10 $ngmL^{-1}$	Serum	[138]
Gal-3	DPV	N- GNRs-Fe-MOFs@AuNPs/ GCE	100 $fgmL^{-1}$ – 50 $ngmL^{-1}$	33.33 $fgmL^{-1}$	Human serum samples	[139]
CEA	DPV	HA/PANI/GCE	0.01 – 10000 $pgmL^{-1}$	0.0075 $pgmL^{-1}$	Serum sample	[140]
PSA	SWV	AuNPs/CTS/SPE	1-18 $ngmL^{-1}$	0.001 $ngmL^{-1}$	Biological samples	[141]
TGF-β1	DPV	AP-Strept-Biotin-anti-TGF- TGF- β1-anti-TGF-SPAuE	0.05 – 3.0 $ngmL^{-1}$	10 $pgmL^{-1}$	Spiked plasma serum	[120]
TNF-α	CV	K-CS-GA/GCE	0.02-34 $ngmL^{-1}$	10 $pgmL^{-1}$	Human serum samples	[142]
CDH 22	EIS, CV	PT-GMA/ITO electrode	0.01-3 $pgmL^{-1}$	3.2 $fgmL^{-1}$	Human serum	[143]
Seratonin	DPV	GO/CTS/SPE	10 nM-100 μM	3.2 nM	Human serum, saliva, artificial tears and urine samples	[144]
CA125	DPV	rGO/Thi/AuNPs/paper based electrode	0.1 UmL^{-1}-200 UmL^{-1}	0.01 UmL^{-1}	Serum sample	[145]
anti- hantavirus	CV	BSA/hantavirus/EDC/ NHS/MPA/ Au electrode	0.400-300 μgmL^{-1}	NS	Spiked serum samples	[146]
monensin	CV	Abs /AuNPs/Zn/Ni-ZIF-8-800@graphene/GCE	0.25–100 $ngmL^{-1}$	0.11 $ngmL^{-1}$	Milk	[147]
DHEAS	EIS	ox-GCE/AuNPs-ARG/IgM	10.0 – 110.0 μgdL^{-1}	7.4 μgdL^{-1}	Patient plasma sample	[148]
brucellosis	DPV	GSH/HA/ OMP31/ AuNPs/GCE	2.08 $fgmL^{-1}$- 1.04 $pgmL^{-1}$	0.50 $fgmL^{-1}$	Diluted serum sample	[119]
gliadins	CV	CNF/SPE	NS	0.005 $mgkg^{-1}$	Food samples	[149]
EpCAM	CV	Anti-EpCAM/SA/G6 PAMAM)/MPA/ Au electrode	1×10^4 – 1×10^6 $cellsmL^{-1}$	2.1×103 $cellsmL^{-1}$	Serum sample	[150]
AFP	DPV	AuPt-vertical graphene/GCE	1 $fgmL^{-1}$-100 $ngmL^{-1}$	0.7 $fgmL^{-1}$	Human serum	[151]
CRH	EIS	Ab/AuNps/Au electrode	10.0–80.0 μgmL^{-1}	2.7 μgmL^{-1}	Real sample	[152]
HCG	DPV	Au-Mab-hCG/SWCNT modified SPCE	10-1000 $pgmL^{-1}$	5 $pgmL^{-1}$	Buffer	[153]
E. coli O157:H7	CV	Au@PtNPs/NR/ rGO/ PANI/AuNPs SPCE	8.9×10^3– 8.9×10^9 $CFUmL^{-1}$	2.84×10^3 $CFUmL^{-1}$	Milk sample Pork sample	[154]
BNP	DPV, CA	GS/SnO2/PANI-Au electrode ZnCo2O4/N-CNTs electrode	0.01 $pgmL^{-1}$ – 1 $ngmL^{-1}$	3.4 $fgmL^{-1}$	Human serum sample	[155]
NMP22	DPV	rGO-TEPA/ AuNPs-PtNPs-MOFs/GCE	0.005- 0.5 $ngmL^{-1}$ 0.5 – 20 $ngmL^{-1}$	1.7 $pgmL^{-1}$	Human urine sample	[156]

(*continued*)

Table 3. Continued.

Analyte	Method	Substrate	Linear range	*LOD/LOQ*	Application	Ref.
HSA	EIS	Au NCs/Ab-HSA/PS-AgNS/ SPCE	30–300 μgmL^{-1}	NS	Spiked buffer	[157]
IFN-γ	EIS	PANI/graphene/SPCE	5-1000 $pgmL^{-1}$	3.4 $pgmL^{-1}$	Human serum sample	[118]
HCG	SWV	CNOs/AuNPs/PEG nanocomposite modified GCE	0.1 $fgmL^{-1}$ −1 $ngmL^{-1}$	0.1 $fgmL^{-1}$	Human urine sample	[158]
ZEN	DPV	ZEN/BSA/ ZEN-MAb/AP-labeled secondary antibody/1-NP/SPCE	0.25-256 $ngmL^{-1}$	0.25 $ngmL^{-1}$	Real matrices	[159]
Amylin	CA	HRP-Strept-Biotin-AMY-AMY- anti-AMY-pPPA/SPCE	1.0 $fgmL^{-1}$ −50 $pgmL^{-1}$	0.92 $fgmL^{-1}$.	Spiked human serum Urine	[121]
TSH	CV	HRP-Ab/TSH/Ab/TGA/ nano-Au/ ILCPE	0.2 – 90.0 $ngmL^{-1}$	0.1 $ngmL^{-1}$	Serum sample	[160]
IgG	DPV	anti-IgG/P2ABA/SPCE	1.0-50 $ngmL^{-1}$	0.15 $ngmL^{-1}$	Buffer	[161]
p53 protein	EIS, CV	StarPGMA/ITO electrode	0.02–4 $pgmL^{-1}$	7 $fgmL^{-1}$	Real samples	[162]

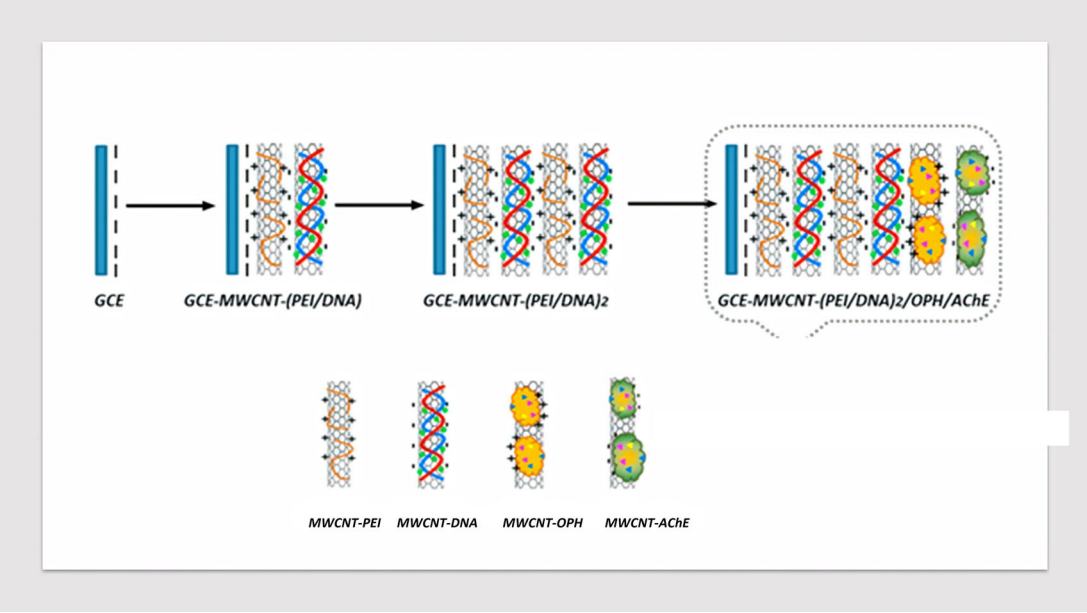


Figure 3. The construction of enzyme based biosensor on GCE for detection of paraoxon as organophosphate and carbaryl as non-organophosphate compounds. Reprinted with permission from.[117]

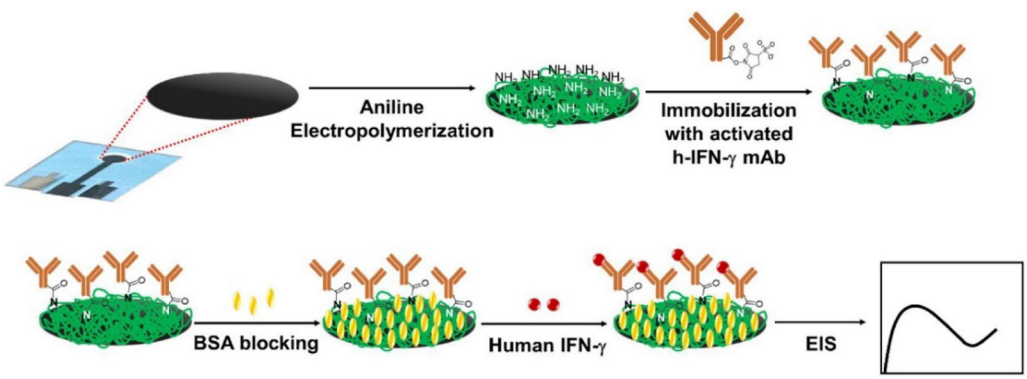


Figure 4. Construction of polymer based immunosensor for detection of IFN-γ biomolecule. Reprinted with permission from.[74]

electrochemical immunosensor is designed using electropolymerized poly(pyrrolepoly(pyrrole propionic acid) (pPPA) on SPCE for the determination of Amylin.[121] HRP-Strept. was used as the enzymatic label. The peak current exhibits a linear response in the range of TSH from 1.0 $fgmL^{-1}$ to 50 $pgmL^{-1}$ and LOD 0.92 $fgmL^{-1.}$ The fabricated immunosensor was applied for the sensitive analysis of TSH in serum sample. Some selected examples on the application of immunosensor based electrochemical biosensors in the literature are listed in Table 3.

Conclusion and future prospects

The ultrasensitive, selective, accurate, cost effective biosensor platforms have been fabricated for detection of very wide range analytes. Further developments on nanomaterials and polymers have shown improvement on response and selectivity. This review demonstrated the wide applicability of electroanalytical biosensors in different areas. Although the disposable electrodes are frequently used in recent years, modifications of electrodes have been studied wider due to their higher surface area and enhanced catalytic action. The validation procedures have demonstrated to their applicability for real samples. DNA based biosensors could be used for the study of drug interaction, analysis of genes and hybridization.[163,164] Amperometric and voltammetric techniques have been preferred by researchers. With the rapid development of immunological agents and equipment, immunosensors are used for the diagnosis and determination of a wide variety of analytes. Immunosensor based sensors are also very promising biosensors with their easy measurement of current, resistance, signal of antibodies, antigens and other biological compounds. Easy-to-use, inexpensive and reliable immunosensing systems have been introduced to a wider area, such as immunoassay technology, medical monitoring, large screening programs and remote environmental monitoring. With increasing interest in nanotechnology, the tattoo and wearable chips and sensors have been studied to detect diseases at early stages. They have shown rapid warning capability. They can also prevent any chemical attacks so that they can be so useful in various fields such as military, industry and agriculture. Multiplexed multidetection of several targets (by incorporation of different enzymes,[165,166] biological materials, DNA, etc on the same transducer or an array of transducers) is a promising field of research.

Research into electrochemical biosensors has been trendly rising up. In the near future, electrochemical biosensor will be further got a handle on medicine, early disease diagnosis, environmental monitoring, food industry and sewage water so on. The development of wearable and self-powered devices fabrication is playing a key role. Moreover, wireless real-time data collection is related closely with electrochemical biosensor development. biosensors and biochips can be used as Point of Care (POC) instruments. Improvement of DNA biosensor will be given information about future prospects for molecular diagnostics. With the rapid progress in the electrochemical biosensing world, it can be envisaged that DNA biosensors without PCR amplification will soon be on the market. Future innovative research on nanomaterials will couple with other major technological advance, such as lateral-flow, lab-on-chip, and 3D printing techniques for the development of next-generation biosensors. Future research on nanozymes in the development of electrochemical biosensors will be used as their commercial applications. This review will also provide powerful insights to researchers for the future development of immunosensors, as well as their broader application in different fields, such as analytical chemistry, food safety control, clinical diagnostics, and environmental monitoring.

Abbreviations

1-NP	1-napthyl phosphate
DSP	3,3′-di- thiodipropionic acid di(n-hydroxy-succinimide ester)
PTCA	3,4,9,10-perylene tetracarboxylic acid
MPA	3-mercaptopropionic acid
HOOC-Phe	4-carboxyphenyl
MPAA	4-mercaptophenylacetic acid
AChE	Acetylcholinesterase
AdSV	Adsorptive stripping voltammetry
Alp	Alkaline phosphatase
AFP	Alpha-fetoprotein
APTES	Aminopropyltriethoxy silane
Abs	Antibody
G6 PAMAM	Amino-terminated polyamido-amine dendrimer
ASV	Anodic stripping voltammetry
ATO-CTS	Antimony tin oxide-chitosan
AuNPs-ARG	Arginine-functionalized gold nanoparticles
S-Phe	Aryl diazonium salt using 4-aminothiophenol
Au NCs	Au nanocrystals
BA	Benzaldehyde
Biotin	Biotinylated
BC	Bismuth citrate
([BSmim]HSO_4	honeycomb-like hierarchically ion liquids
SB	Block T20
BSA	Bovine serum albumin
BNP	B-type natriuretic peptide
CDH 22	Cadherin-like protein 22
CA125	Cancer antigen 125
CA 15-3	Cancer antigen 15-3
CGL	Carbon graphite lead
CNF	Carbon nanofibers
CNT	Carbon nanotube
CPE	Carbon paste electrode
CEA	Carcinoembryonic antigen
cTnT	Cardiac Troponin T
CTAB	Cetyltriammonium bromide
CTS	Chitosan
CTS-AuNPs	Chitosan-stabilized gold nanoparticles
CHER	Cholesterol esterase
ChOx	Cholesterol oxidase
CA	Chronoamperometry
CRH	Corticotropin releasing hormone
CRP	C-reactive protein
CK	Creatine kinase
CV	Cyclic voltammetry
CysC	Cystatin C
DAAO	D-amino acid oxidase
DHEAS	Dehydroepiandrosterone sulfate
DPV	Diferential pulse voltammetry

DTSP	Dithiobissuccinimidyl propionate
DWCNTs	Double-walled carbon nanotubes
bi-SPCE	Dual screen-printed carbon electrodes
EIS	Electrochemical impedance spectroscopy
ERGO	Electrochemically reduced graphene oxide
EpCAM	Epithelial cell adhesion molecule
E. coli O157:H7	*Escherichia coli* o157:h7
EA	Ethanol amine
Fe-MOFs	Fe based metal-organic frameworks
fGQDs	Functionalized graphene quantum dots
Gal-3	Galectin-3
GCE	Glassy carbon electrode
GFAP	Glial fibrillary acidic protein
GOx	Glucose oxidase
GA	Glutaraldehyde
GSH	Glutathione
GK	Glycerol kinase
GPO	Glycerol-3-phosphate oxidase
AuNPs	Gold nanoparticles
AuNPs@rGO	Gold nanoparticles and reduced graphene oxide
Au@PtNPs	Gold@platinum nanoparticles
Au-MSNPs	Gold Mesoporous silica nanoparticles
GNRs	Graphene nanoribbons
GO	Graphene oxide
GrONPs	Graphene oxide nanoparticles
GPE	Graphene paste electrode
GS	Graphene sheets
Gr	Graphite
H-amino-rGO	Hemin -amino-reduced graphene oxide
HBsAg	Hepatitis b virus surface antigen
HRP	Horseradish peroxidase
hcG	Human chorionic gonadotropin
HER2-ECD	Human epidermal growth factor receptor 2
IFN-γ	Human interferon-gamma
HA	Hyaluronic acid
IgG	Immunoglobulin
ITO	Indium tin oxide
IL-1β	Interleukin-1 beta
ILCPE	Ionic liquid carbon paste electrode
I-Py	((e)-4-[(4-decyloxyphenyl)diazenyl]-1-methylpyridinium iodide)
K-CTS	$K_3[Fe(CN)_6]$chitosan-glutaraldehyde
LSV	Lineer sweep voltammetry
MB	Mercapto-benzaldehyde
MIP	Molecularly imprinted polymer
Mab	Monoclonal antibody
MUC1	Mucin1
MWCNTs	Multi- walled carbon nanotubes
Myo	Myoglobin
EDC/NHS	N-(3-dimethylaminopropyl)-n-ethylcarbodiimide hydrochloride/ n-hydroxysuccinimide mixture
NCC	Nano- crystalline cellulose
NCP	Nanocomposite
NPs	Nanoparticles
N-CNTs	N-doped carbon nanotubes
N- GNRs	N-doped graphene nanoribbons
NSE	Neuron-specific enolase
NR	Neutral red
NMP22	Nuclear matrix protein 22
OMC-CTS	Ordered mesoporous carbon-chitosan
OPH	Organophosphatehydrolase
OMP31	Outer membrane protein 31
ox-GCE	Oxidized glassy carbon electrode
PGE	Pencil graphite electrode
PtE	Platinum Electrode
P(PDCA)	Poly(2,6-pyridinedicarboxylic acid)
P2ABA	Poly(2-aminobenzylamine)
p(BCP)	Poly(bromocresol purple)
P(GBHA)	Poly(glyoxal-bis(2-hydroxyanil)
pPPA	Poly(pyrrolepropionic acid)
PT-GMA	Poly(thiophene-g-glycidyl methacrylate)
PANI	Polyaniline
PDDA	Poly-dialyldimethylammonium chloride
PEI	Polyethyleneimine
PPO	Polyphenol oxidase
Pp	Polypyrrole
PS-AgNS	Polystyrene core with silver nanoshells
PVA-SPG	Polyvinyl alcohol with styrylpyridinium groups
PSA	Prostate-specific antigen
QDs	Quantum dots
AXL	Receptor tyrosine kinase
rGO	Reduced graphene oxide
SPCE	Screen printed carbon electrode
SPEs	Screen printed electrodes
SPAuE	Screen printed gold electrode
SWCNT	Single-walled carbon nanotube
SWV	Square wave voltammetry
ß-CD	ß-Cyclodextrin
Strept	Streptavidin
S-AP	Streptavidin enzyme
SA	Succinic anhydride
StarPGMA	Tetra armed star-shaped poly(glycidylmethacrylate)
TEPA	Tetraethylenepentamine
TGA	Thioglycolic acid
Thi	Thionine
TSH	Thyroid stimulating hormone
TiO_2NP_s	Titanium dioxide nanoparticles
TGF-β1	Transforming growth factor beta 1
TNF-α	Tumor necrosis factor alpha
UOx	Uricase
ZEN	Zearalenone
ZnONRs	Zinc oxide nanorods

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