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Review Article

Ultrasensitive electrochemical (bio)sensors for therapeutic drug monitoring

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Abstract

Ultrasensitive detection is important for the individualized management of medical therapy, playing a key role for the improvement of life expectancy and quality of life. Implementing personalized medicine represents a complex challenge since it requires the development of new, simple, versatile, and sustainable technologies that offer real-time, accurate, and reliable outputs. With increasing chronic conditions and cancers, as well as excessive use and abuse of medication, there is a strong need for continuous monitoring of therapeutic drugs to prevent toxicity levels in cases of overdose or inefficiency in cases of underdose.

However, to date, only a few easy-to-use monitoring systems are available for trace analysis of therapeutic drugs to help physicians and patients with therapeutic drug monitoring. Here, we critically evaluate recent advances, highlighting the position of electrochemical (bio)sensors on the roadmap towards ultrasensitive detection for personalized therapy.

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Keywords

Ultrasensitive detection, Electrochemical (bio)sensors, Therapeutic drugs, Nanomaterials.

Introduction

According to WHO's 2019 global health estimates between 2000 - 2019, noncommunicable (chronic) diseases accounted for 7 of the top 10 causes of death in the world, among which cancer is the second one [1]. Lower respiratory infections remained the world's most deadly communicable disease, ranked 4th [2]. Today, patients tend to receive a standardized dose, whereas interpatient variation in drug absorption or response can lead to the administration of an incorrect drug dosage, which may cause side effects [3]. Thyroid hormones (TH) play an important role in biological growth, differentiation, development, and metabolism, being linked to increased proliferation in various cancer cell lines [4,5]. Further, a recent study highlighted that high levels of free thyroxine are significantly associated with an increased risk of cancer [6]. Hormone replacement medication is monitored through clinical observation; therefore, there is an urgent need to implement therapeutic drug monitoring with the aim of personalizing the dose for increased therapeutic efficiency and minimal toxic effects [7].

Electrochemical (bio)sensors provide a low-cost, sensitive, real-time, portable, and convenient solution for the detection of various analytes in biomedical applications by easily achieving low detection limits (LOD) [8]. Reviews by H. Liu and X. Tong highlight recent progress in electrochemical (bio)sensors for health monitoring [9,10]. Significant progress was also made towards tailoring composite nanomaterials (NM) to have controllable morphologies and dimensions, surface charges, and physicochemical properties that increase sensitivity and specificity for the ultrasensitive detection of pharmaceuticals, as comprehensively illustrated by the works of L. Qian and M. Negahdary [11,12]. Other reviews specifically target the use of tailored NMs for antibiotics [13] or analgesics [14], thus exploring the multifunctional role of nanomaterials.

This review will endeavor to provide new insights and guidance towards the development of more efficient, simple, sustainable, and customizable electrochemical (bio)sensors for therapeutic drug monitoring. The focus will be on the ultrasensitive detection of three classes of pharmaceuticals, used for communicable and noncommunicable diseases and replacement treatments, highlighting the outstanding performances of electrochemical (bio)sensor architectures.

Ultrasensitive detection of antibiotics

The term *antibiotic* usually refers to antimicrobial drugs that "kill" any kind of microbe or "prevent the growth" of bacteria [15] and are among the drugs that are often

abused. Pathogenic microbes can develop ways to avoid antibiotics, increasing the risk of hard-to-treat infections [16], and yet, not many electrochemical, portable (bio) sensors are available.

The synergy between simple architecture and ultrasensitive detection is not easy to achieve, yet W.D. Adane managed to develop a simple, sensitive, costeffective, and environmentally friendly sensor using choline chloride (ChCl) electrodeposited on a carbon paste electrode (CPE), which promoted electron transfer for the detection of ciprofloxacin [17]. The detection methods and parameters for the described sensors are presented in Table 1. Ciprofloxacin was also detected with a biosensor based on complementary strands of aptamer (CSs) and methylene blue (MB) as a redox and labeling agent to obtain a double-labeled aptamer as a sensing probe. The ingenuity of this system lies in its capability to surpass the CSs lying flat on the surface of the gold electrode, which decreases sensor sensitivity [18]. Another aptasensor with good reusability and long-term storage stability attained by simply rinsing the sensor in deionized water was developed for ampicillin. Precise control of the surface nanospacing of the aptamer probes was obtained by self-assembled tetrahedral DNA nanostructures (TDN) [19]. Norfloxacin (NOR), a fluoroquinolone antibiotic, was detected by a nickel-cobalt (Ni−Co) metal-organic framework (MOF) modified with pure nickel foam (NF). The composite material itself (ultrathin nanosheets) served as a working electrode with a unique, flexible, and antifouling sensing surface [20]. G. Li developed a sensor for NOR with an intriguing design: gold nanoparticles (AuNP)-decorated black phosphorus nanosheets (BPNS) were drop-casted on a glassy carbon electrode (GCE) that was followed by electropolymerization of a molecularly imprinted polymer (MIP) film of pyrrole as described in Ref. [21].

Two types of porous organic polymers (POP) were constructed by the group H. He. For the first POP configuration, covalent bonding between two monomers (1, 3, 6, 8-tetraphenylpyrene, and α, α′-dibromo-p-xylene) was achieved through polymerization. The obtained surface shows outstanding physicochemical stability and high porosity binding with increased efficiency aptamers for ampicillin detection [22]. For the second POP configuration, 2,4,6-tri(9H-carbazol-9-yl)-1,3,5-triazine and 2,4,6-tris(bromomethyl) mesitylene were reacted by Friedel – Crafts coupling reaction, followed by aptamer immobilization for specific penicillin detection [23]. For the ultrasensitive detection of sulfadiazine, a nanocomposite based on graphite oxide (GO) and rare-earth metal (gadolinium vanadate - $GdVO_4$) was synthesized through a hydrothermal process reinforcing a GCE for superior selectivity and sensitivity [24]. From the same class of antibiotics, sulfamethoxazole was indirectly quantified in serum samples using a nanocomposite obtained through simple *in situ* precipitation synthesis of multiwalled carbon nanotubes (MWCNTs) decorated with silver oxide nanoparticles (Ag_2O) [25].

Kanamycin can interfere with protein synthesis; thus, Huang W. employed a homogeneous biorecognition reaction to induce the assembled formation of DNA nanostructures (NSs) at the electrode surface. Of increased interest is the use of exonuclease I, which can produce hairpin DNA but also causes target recycling. Further, dual signal amplification was achieved by the presence of AuNP/HRP (horseradish peroxidase-functionalized AuNP) nanotags [26]. A more facile approach was developed by F.K. Algethami by allowing a layer-by-layer deposition of a melanin-like polymeric film (MLPF) on an electrode surface modified with AuNPs employing electrochemical capacitance spectroscopy (ECS) [27].

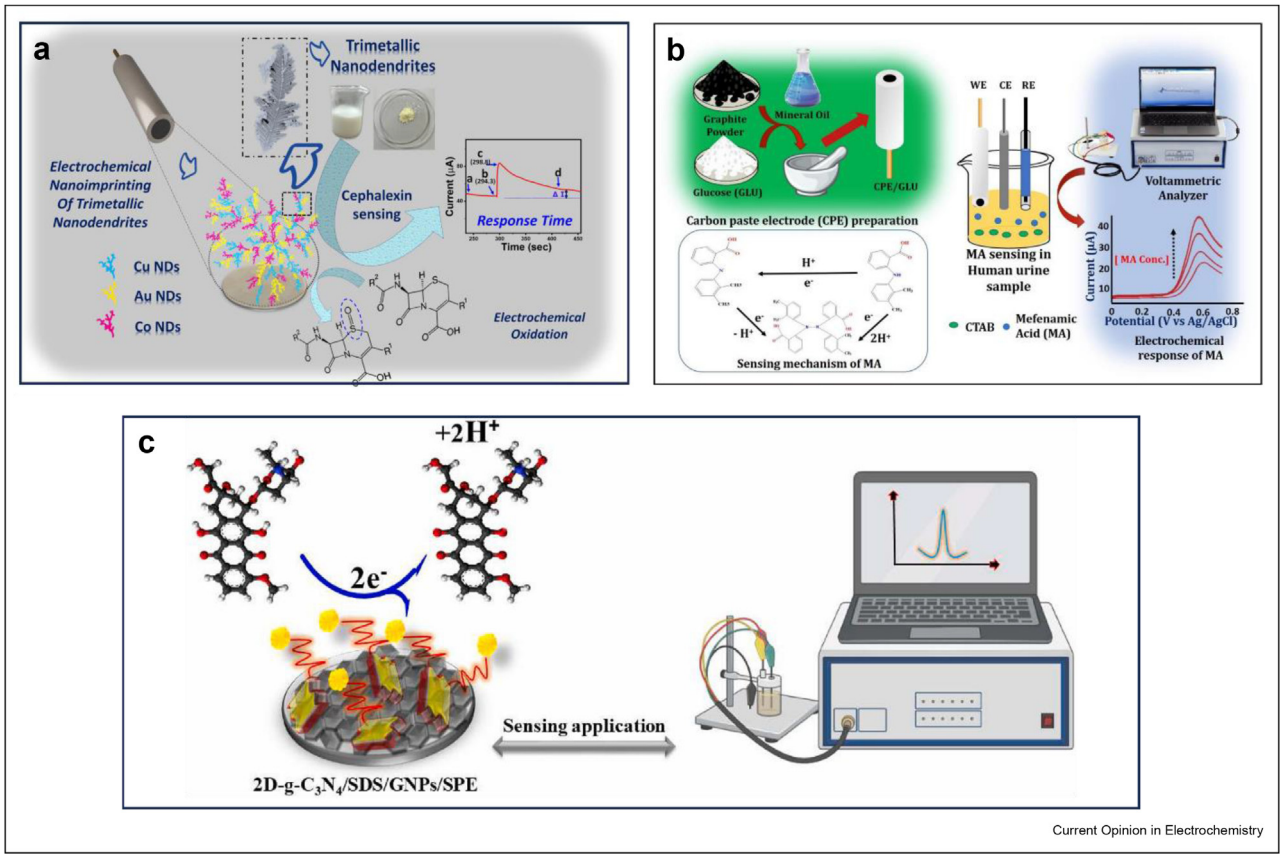
Table 1

Architecture and performances of (bio)sensors for antibiotics detection.

(Bio)sensor	Method	Analyte	LOD	Reference
ChCl/CPE	SWV	ciprofloxacin	0.36 nM	[17]
CS1/MB-Apt-MB/CS2	DPV	ciprofloxacin	0.10 nM	[18]
ErGO-SPE/AuNPs/TDN	DPV	ampicillin	1.0 pM	[19]
Ni−Co-MOF NF	DPV	norfloxacin	22.29 nM	[20]
MIP/BPNS-AuNP/GCE	LSV	norfloxacin	0.012 nM	[21]
apt/POP/AE	EIS	ampicillin	3.30 fM	[22]
apt/POP/AE	EIS	penicillin	0.32 pg/mL	[23]
$GdVO_4$@GO/GCE	amperometry	sulfadiazine	3.1 nM	[24]
Ag_2O@MWCNTs/GCE	DPV	sulfamethoxazole	4.06 pM	[25]
AuNP-HRP/MB/DNA-NS/Au	DPV	kanamycin	9.1 fg/mL	[26]
Apt/MLPF/AuNPs/SPCE	ECS	kanamycin	0.3 fM	[27]
GCE/AuCoCu NDs	amperometry	cephalexin	0.04 nM	[28]

SWV – square wave voltammetry; Apt-aptamer; DPV – differential pulse voltammetry; LSV – linear scan voltammetry; AE – gold electrode; EIS – electrochemical impedance spectroscopy; ErGO-SPE - electrochemically reduced graphene oxide modified screen printed electrode; AuCoCu NDs – gold, cobalt, and copper nanodendrites.

Figure 1



(Bio)sensor architectures and working principles for ultrasensitive analyte detection: **a.** Schematic representation of the nanoimprinting of a trimetallic dendritic sensing probe and detection of cephalexin (CFX) [28]. Reprinted with permission from MDPI (mdpi publisher (https://www.mdpi.com/)); **b.** Illustration of sensor fabrication and working principle for the determination of MA [36]; **c.** The proposed electrochemical mechanism for the oxidation of doxorubicin (DOX) at 2D-g-C_3N_4/SDS/GNPs/SPE [43]. GNPs, graphene nanoplatelets; SDS, sodium dodecyl sulfate; SPE, screen printed electrode. Reprinted with permission from Elsevier.

For the detection of cephalexin, one of the most used drugs, and for which bacteria have developed resistance, R. Kumari and P. Chandra developed a unique trimetallic dendritic NS comprised of cobalt, copper, and gold. The metals were electrochemically imprinted on a GCE surface for a simple and robust sensor with superior catalytic properties, high stability, and reproducibility, as shown in Figure 1a [28].

Ultrasensitive detection of analgesic and antipyretic drugs

Pain management drugs are divided into two broad categories: nonopioid and opioid analgesic agents. In the nonopioid class are acetaminophen (paracetamol - PAR) and nonsteroidal anti-inflammatory drugs (aspirin, ibuprofen, and mefenamic acid), which are used for mild-to-moderate pain associated with inflammation and fever [29], in the treatment of various diseases, including communicable diseases [30,31].

Multianalyte sensing is important, especially for the elderly with several medical conditions where treatment monitoring plays an important role. H.S. Sawan accomplished the simultaneous early detection of PAR and metoclopramide using a novel nanocomposite, with sensor performances shown in Table 2. Zirconium dioxide (ZrO_2) NPs and an ionic liquid (IL:1-hexyl-3-methylimidazolium hexafluorophosphate) were mixed into the CPE composition to achieve enhanced electron transfer [32]. With increased long-term stability but lower sensitivity, PAR was successfully quantified with the help of novel swollen 1 T/2H hybrid phases of molybdenum disulfide (MoS_2) with a walnut-like fold nanostructure anchored in situ on rGO nanosheets [33]. Another sensor for simultaneous detection of PAR and 4-aminophenol was developed by X. Niu, who tested a series of bimetallic cobalt-nickel alloys coated with nitrogen-doped carbon composites (CN derived from MOF) dispersed in Nafion solution and dropped on a

Table 2

Architecture and performances of (bio)sensors for pain relievers.

(Bio)sensor	Method	Analyte	LOD	Reference
ZrO_2NP/IL/CPE	SWV	paracetamol	28 pM	[32]
		metoclopramide	29 pM	
MoS_2/rGO/GCE	DPV	paracetamol	1.7 nM	[33]
Co_1Ni_1@CN-700/GCE	DPV	acetaminophen	3.8 nM	[34]
		4-aminophenol	5.2 nM	
NHCS-1000/GCE	DPV	acetaminophen	95.0 nM	[35]
GLU/CPE	SWV	mefenamic acid	1.01 nM	[36]
CVO/RGO/GCE	DPV	mefenamic acid	7.9 nM	[37]
AgNPs@Af-GO-MIP/GCE	DPV	ibuprofen	8.7 nM	[38]
SPCE/(Cs + AuNPs)	CV	aspirin	0.03 pg/mL	[39]

SWV – square wave voltammetry; DPV – differential pulse voltammetry; CV, calcium vanadate.

GCE [34]. Simultaneous sensing of PAR, dopamine, uric acid, and ascorbic acid was achieved by Duraisamy V. on a graphitized porous carbon-modified electrode using an N-doped hollow carbon sphere (NHCS) [35].

For mefenamic acid (MA) detection, P.R. Vernekar developed a very simple approach: glucose (GLU) being mixed in the composition of a negatively charged particles (CPE). Electrochemical measurements were performed in the presence of cetyltrimethyl ammonium bromide (CTAB), which adsorbed on the electrode surface, allowing a preconcentration step for MA and enhancing the stability and sensitivity of its detection, as presented in Figure 1b [36]. A more complex sensor architecture was based on calcium vanadate ($Ca_{10}V_6O_{25}$ – CVO) nanofilaments embedded on rGO. Enhanced catalytic properties were obtained due to the structural defects in the rGO nanosheets, while the durability of CVO assured the robust reproducibility and long-term stability of the sensor [37]. A greener approach was employed by A.S. Nair and M.P. Sooraj, who obtained a silver nanoparticle-decorated acidic-functionalized GO (AgNPs@Af-GO) composite in the presence of *Caesalpinia sappan* leaf extract and used it as a MIP-modified composite sensor for the detection of ibuprofen. Even though an elaborated process was necessary for the sensor fabrication, its performance was successfully validated, with the added benefits of cost effectiveness and faster detection [38]. Quantitative detection of aspirin was achieved by a simple self-assembling technique of chitosan (Cs)-capped AuNPs on SPE. A solution of Cs and chemically synthesized AuNPs was drop-casted on screen-printed carbon electrode (SPCE) and subjected to cyclic voltammetry for electrodeposition [39]. A more recent approach for aspirin detection based on an electrode modified with one-dimensional $Cu(OH)_2$/carboxymethyl cellulose (CMC) composite nanofibers has been developed, with a LOD = 0.1 μM [40].

Ultrasensitive detection of chemotherapeutic drugs

Dosing anticancer drugs at low concentrations and detecting them with high sensitivity is of great importance for therapy monitoring [41]. Analytical performance of (bio)sensors can be enhanced by tailoring various NMs; thus, oxygen functional groups at graphene nanosheets (GRNs) synthesized by the metal intercalation-based exfoliation method were exploited. Metallic potassium (M) was used to obtain black M-GRNs powder, which was dispersed in an aqueous dimethylformamide (DMF) mixture and drop-casted on a SPCE [42]. M. Mehmandoust achieved sensitive detection of doxorubicin using combustion methods to prepare 2-dimensional graphite nitride (2D-g-C_3N_4), which was further mixed with graphene nanoplatelets (GNPs), added into sodium dodecyl sulphate (SDS) aqueous solution, and drop-casted onto a SPE. SDS was used as an anionic surfactant agent, attracting the analyte to the electrode surface and leading to faster electron transfer, as highlighted in Figure 1c [43]. An easier approach was performed by S.I. Kaya through the ultrasonication method of ruthenium (Ru) and vulcan carbon (Vc) in ethanol, with the later addition of 4-(dimethylamino) benzaldehyde (DMAB). The aqueous suspension was drop-casted onto GCE, and the obtained sensor showed good analytical performances in human serum samples (LOD = 7.4 nM) (Table 3) [44]. A simultaneous detection of anticancer drugs was achieved by a multifunctional nanocomposite based on binary transition metal sulfide nanoparticles, $CuCo_2S_4$, with increased conductivity and rich redox reactions, further enhanced by magnetic NPs of iron oxide (Fe_3O_4). A well-defined peak separation in DPV was achieved due to this easily obtained nanocomposite [45]. Ultrasensitive detection of methotrexate (MTX) relies on electrografting, MIP technologies, and nanomaterials. D. Mwanza chose to electrodeposit 5-diazonium

Table 3

Architecture and performances of (bio)sensors for anticancer drugs.

(Bio)sensor	Method	Analyte	LOD	Reference
M-GRNs/SPCE	DPV	pemetrexed	9.7 nM	[42]
2D-g-C_3N_4/SDS/GNPs/SPE	DPV	doxorubicin	10 nM	[43]
Ru@Vc/GCE	DPAdSV	idarubicin	9.25 nM	[44]
Fe_3O_4@$CuCo_2S_4$/GCE	DPV	topotecan	6.94 nM	[45]
		mitomycin	80 nM	
GCE-IPA-Ab	EIS	methotrexate	7.0 pM	[46]
SPCE-IPA-Ab			5.5 pM	
MIP/MWCNT/GCE	DPV	methotrexate	2.7 nM	[47]
Au@f-NCB/MW-GCPE	SWAdASV	formestane	7.14 nM	[48]
		doxorubicin	7.40 nM	
IL/Au@GCNFs-PE	SWV	irinotecan	1.55 nM	[49]

DPAdSV - Differential pulse adsorptive stripping voltammetry; SWAdASV - Square-wave adsorptive anodic stripping voltammetry; DPV – differential pulse voltammetry; EIS – electrochemical impedance spectroscopy; SWV – square wave voltammetry.

isophthalic acid (5-DIPA) as a thin monolayer for the immobilization of anti-methotrexate polyclonal antibody (Ab) on both GCE and SPCE electrodes. Both configurations were employed in capacitive EIS, and the obtained data led to very low LODs, as presented in Table 3. This work clearly illustrates the possibility of miniaturization and extension of its application towards Point-of-Care (POC) analysis [46]. A more recent approach for MTX detection with a higher LOD of 2.7 nM was based on a MWCNT-modified GCE [47]. M.A. Hazim developed a molecular wire glassy carbon paste electrode (MW-GCPE) modified with AuNP-decorated carboxyl functionalized nanocarbon black (Au@f-NCB) through drop-casting. The sensor was used for formestane detection in the presence of a fixed concentration of doxorubicin, with LODs of 8.0 nM in human urine and 8.14 nM in serum samples, with excellent sensitivity, stability, recovery, and antifouling properties [48]. H. Ibrahim and Y. Temerk developed an electrochemical sensor for the determination of irinotecan: AuNPs were anchored on graphitized carbon nanofibers (Au@GCNFs), mixed with paraffin oil, and conductive IL [BMIM]PF6 to obtain a paste electrode (PE). A slight increase of the LOD to 1.7 nM, with good resolution and potential separation was observed in the presence of quaternary analytes that coexist in serum samples, highlighting the development of a simple, stable, and low-cost sensor [49].

Ultrasensitive detection of drugs used in replacement therapies

Since replacement therapies for thyroid-related conditions are significantly associated with an increased risk of cancer, (bio)sensors for the detection of replacement THs, such as levothyroxine (LT4) and triiodothyronine (T3), present importance. For free T3 (FT3) detection, a biosensor based on GCE modified with Fe_3O_4@graphene nanocomposite, high-affinity fT3 antibodies, and laccase, which catalyzed the redox reaction of FT3, was developed [50]. A complex architecture was employed, and the biosensor presented an LOD of 27 nM, which is higher than the normal values for a healthy adult (4.6–9.7 pM) [51]. FT3 levels are often correlated with LT4 levels. A literature search for the detection of LT4 for the last two years only found two sensor configurations, which were developed in our previous works. Optimizing the working parameters for DPV detection of LT4, LODs of 30 nM in acetate buffer (pH 4.0) and of 23 nM in diluted bovine serum were obtained [52]. With the impedimetric sensor modified with $NiCo_2O_4$ (nickel-cobalt oxide) NPs loaded on rGO sheets, an LOD below normal physiological levels (12–30 pM [53]) was achieved. The $NiCo_2O_4$@rGO nanomaterial was dispersed in Nafion and drop-casted on commercial SPCE. By monitoring the capacitance of the system, an LOD of 6.1 pM was calculated [54]. Such a low LoD represents an excellent achievement and could be regarded as a first step towards developing a simple POC system for patients with cancer and thyroid gland dysfunction.

Shortcomings and new directions

Herewith, we can conclude that the tendency to develop ultrasensitive (bio)sensors for trace analysis over the past few years for therapeutic drugs is of great importance. More and more drugs like antibiotics, paracetamol, aspirin, and ibuprofen are abused, causing toxic side effects. Hormone replacement therapies (for thyroid diseases but also for menopause) are widely used, and monitoring the effectiveness of treatment is required because incorrect doses may be associated with an increased risk of cancer.

It is not enough to only consider the development of sensitive and specific real-time monitoring platforms or POC systems based on (bio)sensors; it is also necessary

to consider environmental and societal aspects such as the use of less toxic compounds, green technologies for nanomaterial synthesis, and cost-effective methods. Few of the above (bio)sensor architectures presented simplicity and reduced carbon footprints through the fabrication methods, while none of the articles considered a solution for disposal of the single-use (bio)sensors, which are predominant. Few architectures presented a robust configuration for multiple uses, and usually those architectures were not yet implemented as POC systems. Biocompatible and biodegradable (bio) sensors must be considered; a simple cleaning and/or regeneration step must be introduced to assure reusability. A few examples in this direction could be the application of a potential to remove the analyte from the surface or the use of an antifouling film. Another aspect that could be considered is a "closed loop system" that would assure not only drug monitoring but also drug delivery, as already implemented for patients with diabetes. Wearable sensors are also an emerging alternative for continuous monitoring; however, they are currently implemented for few analytes. Advantages and limitations of (bio)sensors should also be considered toward classical, more sensitive techniques such as high-performance liquid chromatography, enzyme immunoassays, or chromatography-mass spectrometry, which offer increased sensitivity in complex matrices; however, they have the limitations of cost and specialized personnel. On the other hand, (bio)sensors are easy to use and offer a real-time response, but high backgrounds and multicomponents may limit accuracy and sensitivity.

Thus, implementing drug monitoring to avoid overdosage or underdosage for personalized treatment for patients with communicable and noncommunicable diseases and replacement treatments will be essential in the future. Technology rapidly evolves towards personalized medicine, and electrochemical (bio)sensor will play a crucial role.

Author contributions

Conceptualization: M.F and M.D; Data curation: M.F and M.D; Formal analysis: M.F and M.D; Supervision: M.F; Visualization: M.F and M.D; Roles/Writing - original draft: M.D; and Writing - review &; editing: M.F.

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.

Data availability

No data was used for the research described in the article.

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** of outstanding interest

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