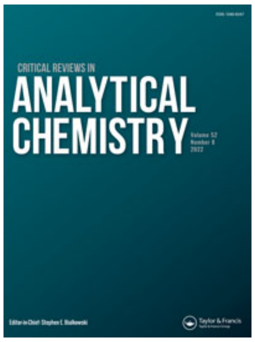

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Recent Advances in Metal Nanocomposite-Based Electrochemical (Bio)Sensors for Pharmaceutical Analysis

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ABSTRACT
Rising rates of drug abuse and pharmaceutical pollution throughout the world as a consequence of increased drug production and utilization pose a serious risk to public health and to environmental integrity. It is thus critical that reliable analytical approaches to detecting drugs and their metabolites in a range of sample matrices be developed. Recent advances in the design of nanomaterial-based electrochemical sensors and biosensors have enabled promising new approaches to pharmaceutical analysis. In particular, the development of a range of novel metal nanocomposites with enhanced catalytic properties has provided a wealth of opportunities for the design of rapid and reliable platforms for the detection of specific pharmaceutical compounds. The present review provides a comprehensive overview of representative metal nanocomposites with synergistic properties and their recent (2017–2022) application in the context of electrochemical sensing as a means of detecting specific antibiotic, tuberculostatic, analgesic, antineoplastic, antipsychotic, and antihypertensive drugs. In discussing these applications, we further explore a variety of testing-related principles, fabrication approaches, characterization techniques, and parameters associated with the sensitivity and selectivity of these sensor platforms before surveying the future outlook regarding the fabrication of next-generation (bio)sensor platforms for use in pharmaceutical analysis.

KEYWORDS
Biosensors; electrochemical sensors; metal; nanocomposites; pharmaceutical analysis

1. Introduction

The expanding and aging of the global population has spurred an increase in overall pharmaceutical consumption aimed at treating a range of chronic and age-related diseases. By the end of 2020, global pharmaceutical revenues were estimated to exceed \$1.27 trillion USD.[1] Owing to limited or inadequate regulation and associated issues, rates of drug abuse and pharmaceutical pollution have also risen rapidly in recent decades such that they have emerged as an epidemic in many nations, endangering both public health and environmental integrity.[2–4] The pharmaceutical contamination of aquatic environments, in particular, can directly harm the organisms therein even when present only at relatively low concentrations.[5] There is thus a clear need for the development of reliable approaches to detecting pharmaceutical agents and their metabolites in a range of sample matrices. Sensitive pharmaceutical analysis platforms would also be invaluable in the context of drug development, clinical trial monitoring, forensic testing, quality control, and environmental monitoring. At present, some of the most widely utilized methods for the detection of pharmaceutical agents include spectroscopy,[6] capillary electrophoresis,[7] liquid chromatography-mass spectrometry (LC-MS),[8] and high-performance liquid chromatography (HPLC).[9] These techniques, however, require specialized instrumentation and skilled personnel to implement, limiting their routine usage. There have been several advances in the design and application of electrochemical (bio)sensors over the past two decades with the potential to replace these cumbersome approaches for the majority of pharmaceutical analysis.

Electrochemical (bio)sensors are robust analytical platforms that offer key advantages including being self-contained, inexpensive, and portable owing to their incorporation of a variety of novel nanomaterials with advanced properties. Metal nanocomposites, in particular, offer great promise in the design of such sensor platforms owing to their enhanced catalytic activity and to the exotic properties which they exhibit as a consequence of the synergistic interactions among their constituent components. Metal nanoclusters immobilization on graphene, for example, has been shown to result in improvements in electron transfer efficiency and reactant transport within the

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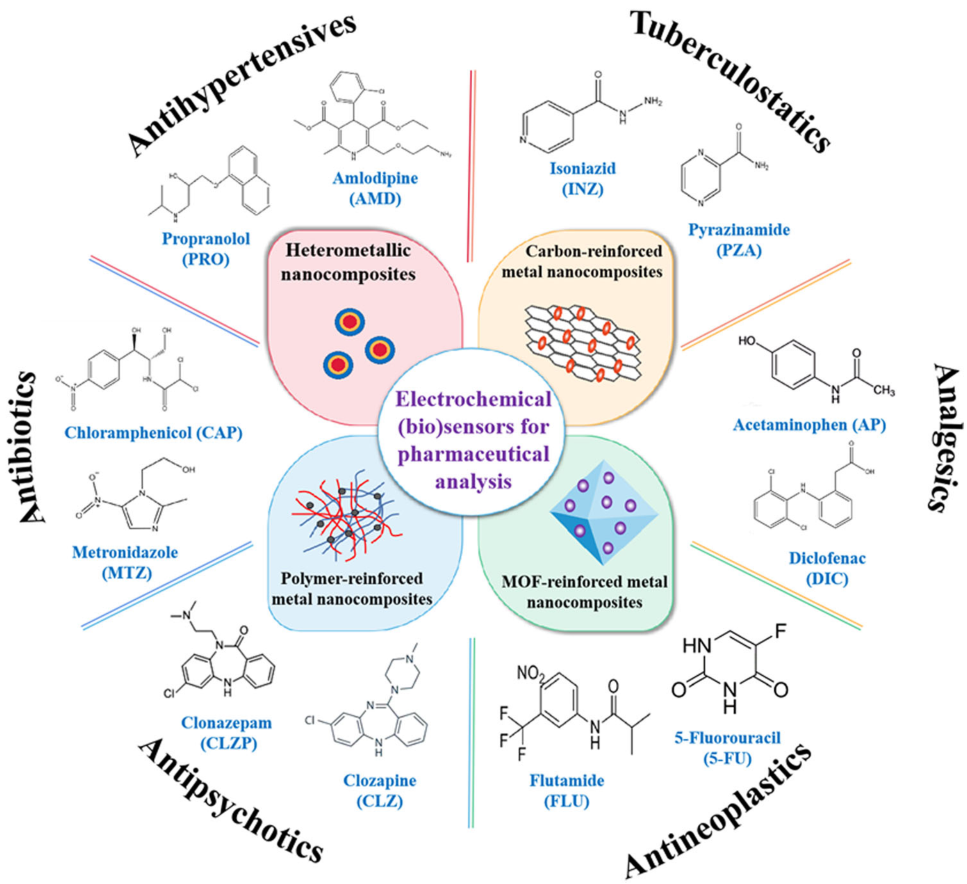

Figure 1. Schematic overview of typical metal nanocomposites and their electrochemical sensing applications for pharmaceutical analysis.

resultant composite material, thereby augmenting catalytic activity levels.[10] Relative to unmodified metal nanoparticles (MNPs), these nanocomposites are also multifunctional and exhibit the potential for extensive surface modification through conjugation with particular materials harboring appropriate motifs,[11] making them widely applicable for the development of a range of electrochemical sensing applications. Owing to these properties, many recent studies have intensively focused on the effective utilization and optimization of a range of functional metal nanocomposites.

Many researchers have reviewed the applications of nanomaterial-based sensors and biosensors for use in the detection of pharmaceuticals.[12–14] While these prior reviews are invaluable, to the best of our knowledge, no comprehensive and systematic review to date has specifically focused on the distinct properties of metal-based nanocomposites owing to the synergistic effects, and a discussion of the recent developments in this field is thus warranted. In the present review, we provide an overview of the most recent advances in the development of metal nanocomposite-based electrochemical sensors and biosensors for use in the detection of a variety of pharmaceutical compounds in various pharmaceutical, biomedical, and biological contexts, with a primary focus on the period from 2017 to 2022. We begin by discussing the electrochemical approaches most commonly employed for measurement purposes in the context of pharmaceutical analysis, after which we explore typical metal nanocomposites and their unique properties that make them well-suited to the development of efficient and sensitive electrochemical (bio)sensor platforms (Figure 1). In the third section, we provide an overview of recent breakthroughs in the design of electrochemical sensor platforms capable of selectively detecting six categories of drugs, after which we close by exploring the challenges facing this field and associated future prospects. Together, this review seeks to provide a robust foundation for improving the analytical performance of nanomaterial-based electrochemical (bio)sensors for future use in the detection of pharmaceutical agents.

2. Electrochemical methodologies employed for pharmaceutical analysis

A prototypical electrochemical sensor is traditionally composed of a three-electrode system including a working electrode (WE), a reference electrode (RE), and a counter/auxiliary electrode (CE or AE), as shown in Figure 2A. The surface of the WE is the site of the primary electrocatalytic reaction of interest, while the CE ensures the completion of the electrical circuit such that current flows between the WE and CE, whereas voltage is applied between the WE and RE. The RE serves to enable the control of applied potential based upon a stable reference reaction. All three of these electrodes must be chemically stable and conductive. The WE and CE are thus commonly designed using gold (Au), platinum (Pt), or graphite based upon the specific analytical application of interest, while most RE currently use Ag/AgCl or saturated calomel electrode (SCE). Voltammetry and

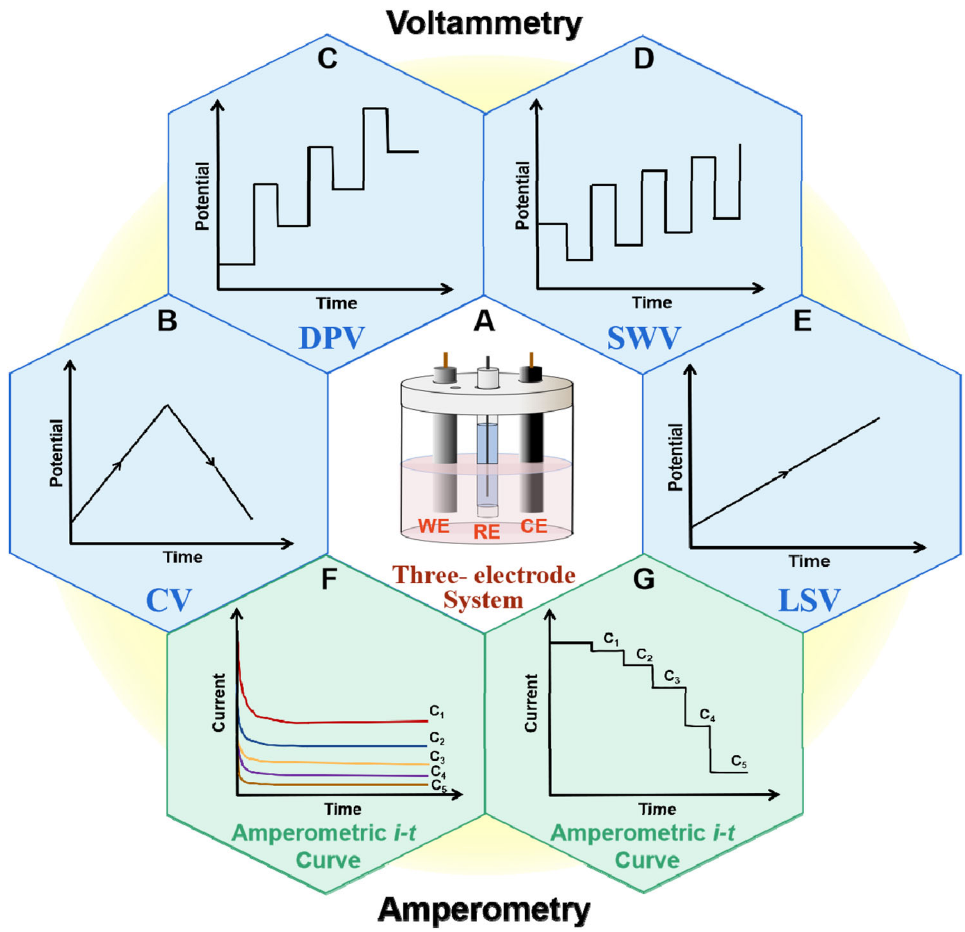

Figure 2. (A) Schematic overview of an electrochemical cell; Schemes for the applied potential in (B) CV, (C) DPV, (D) SWV and (E) LSV; Amperometric *i–t* curves with isolated (F) and subsequent (G) concentration additions of the analyte.

amperometry are the two applied electrochemical techniques that are commonly employed in the context of pharmaceutical analysis, with the former referring to measurements of current during controlled potential variations and the latter referring to measurements of current at a constant potential.[15] In contrast to these two strategies, other techniques such as potentiometry or electrochemical impedance spectroscopy (EIS) are relatively infrequently implemented for such analysis.

The voltammetric approaches employed in the context of drug detection include cyclic voltammetry (CV), differential pulse voltammetry (DPV), square wave voltammetry (SWV), and linear sweep voltammetry (LSV), with the method whereby potential is applied prior to current measurements being the primary difference among these techniques. CV is the most commonly employed approach to exploring electrochemical reaction properties and electrode-related kinetic parameters, relying upon an applied potential that is linear swept at a constant rate, with the cycle being completed upon return to the initial position in the opposite direction (Figure 2B). This approach offers the primary advantage of driving both the anodic and cathodic activity of electrode systems, enabling the monitoring of physicochemical processes associated with redox species such as homogeneous chemical reactions, disproportionation, or adsorption.[16]

DPV and SWV exhibit greater analytical sensitivity and measurement speed as compared to CV owing to the application of pulse techniques, which significantly lower charging current contributions and thereby improve the Faradaic response signal as well as the overall quality of resultant data. DPV employs a series of brief (10–100 ms) superponated pulses of fixed amplitude ($\Delta E = 1–100$ mV), ramping up potential in a staircase-like manner, with current being samples two times before and after the application of each pulse (Figure 2C).[17,18] DPV is well-suited to trace analyses given that it can detect electroactive compounds at concentrations as low as $10^{-7}–10^{-8}$ M.[19] SWV similarly employs a superponated symmetrical square-wave pulse to generate a potential staircase (Figure 2D), providing a limit of detection (LOD) comparable to that of spectroscopic or chromatographic methods. SWV is particularly well-suited to analyzing electrode processes that are reversible or coupled to rapid chemical reactions. In contrast, it is less effective when assessing slower electrode processes, performing poorer than traditional voltammetry for particularly slow processes.[20] LSV is the simplest of these voltammetric techniques, with polarization current being analyzed over time with the application of linearly increasing potential (Figure 2E).

Amperometric electrochemical sensors continuously measure current arising as a consequence of redox reactions

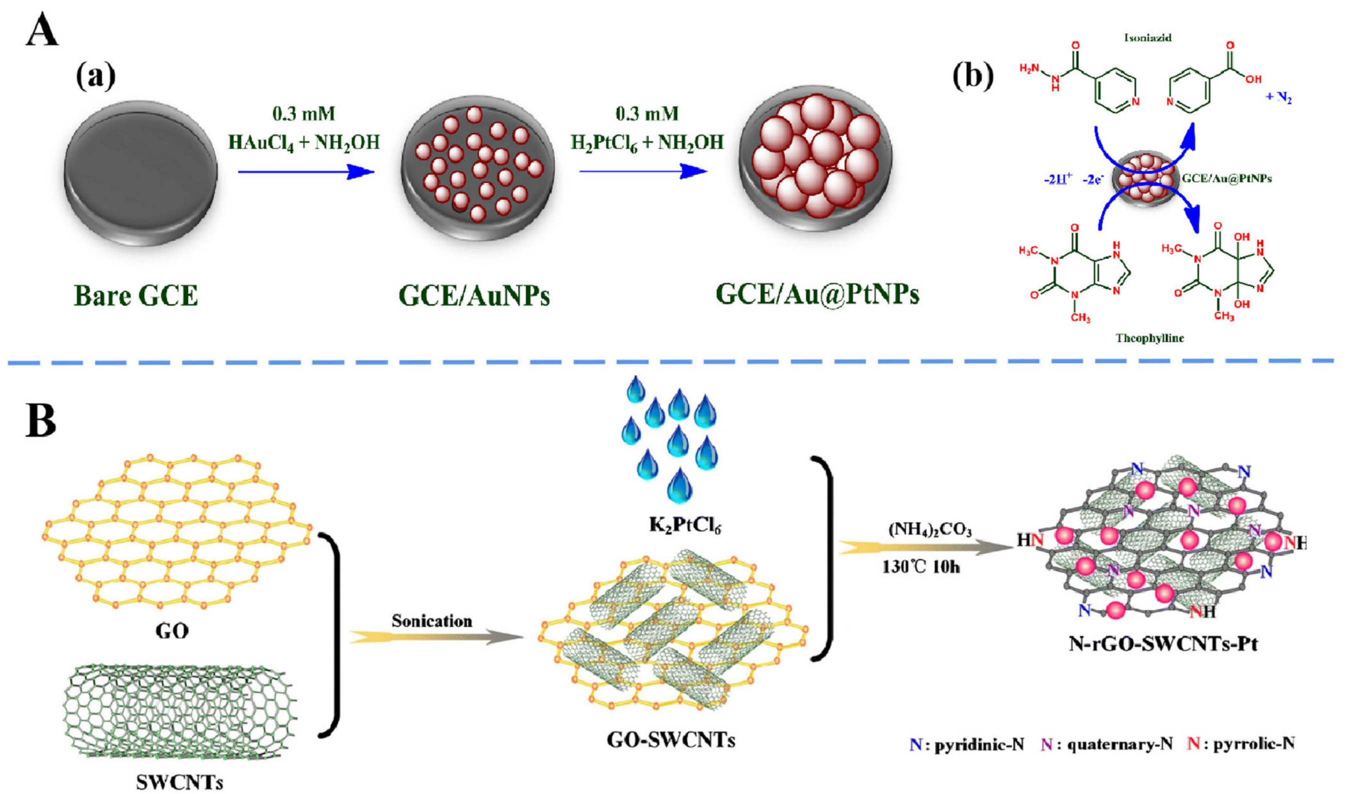

Figure 3. Schematic overview of (A) electroless GCE/Au@PtNPs deposition (a) and INZ and TP electrochemical oxidation at the modified electrode surface (b) (Reproduced from Ref.,[26] with permission from Elsevier); (B) N-rGO-SWCNTs-Pt nanocomposite synthesis (Reproduced from Ref.,[35] with permission from Springer).

observed for an electroactive species at a constant applied potential. The resultant current generally varies with isolated (Figure 2F) or subsequent (Figure 2G) concentration additions of the analyte. A range of amperometric sensors have been discussed in detail in prior reports, offering greater selectivity and a lower LOD than voltammetric sensors. Another modified amperometric sensing technique is known as chronoamperometry in which the WE is subjected to the application of a square-wave potential, which changes in current arising in response to the reductions or increases in analyte diffuse layers at the WE surface.[21] While this approach exhibits certain advantages, it is relatively slow, with many chronoamperometric measurements requiring at least 10 seconds.

3. Metal nanocomposite development for electrochemical (bio)sensors

In an effort to overcome the limitations of individual nanomaterials and homogenous preparations, a range of highly efficient approaches to synthesizing various metal nanocomposites have been developed. Unlike true alloys, the resultant nanocomposites generally retain the properties of their individual constituent components, with their final characteristics arising as a consequence of the filler geometry, filler content, filler arrangements, and matrix-filler interface bonding. Below, we explore four representative kinds of metal nanocomposites employed in electrochemical sensors used to detect pharmaceutical agents.

3.1. Heterometallic nanocomposites

Heterometallic nanocomposites are generated through the nano-scale integration of two or more different metallic components.[22] Owing to synergistic effects arising from the included materials, the resultant composites exhibit excellent physicochemical and electrical properties superior to those of individual MNPs. In addition to the intrinsic properties of the selected nanomaterials, the architectural characteristics of prepared heterometallic nanocomposites have a profound impact on the characteristics of the resultant material. These nanostructures can be synthesized in random structures in which atoms do not exhibit selective orientation, core-shell structures wherein a given nanomaterial serves as a core surrounded by sequential layers of other nanomaterials, or cluster-in-cluster structures wherein one nano-nucleated metal functions as a binder for the others.[23] Many researchers have explored novel approaches to preparing heterometallic nanocomposites of a desired shape, size, and makeup through approaches such as laser ablation, co-reduction, radiolytic synthesis, or thermal decomposition.[24,25] In terms of sensing purposes, these nanocomposites have attracted substantial interest for use in pharmaceutical applications, with enhanced electrocatalytic activity, high stability and even good biocompatibility. Gowthaman et al., for example, utilized a glass carbon electrode (GCE) modified with Au-Pt core-shell nanoparticles (Au@PtNPs) as a tool to detect levels of isoniazid (INZ) which is a tuberculostatic drug[26] (Figure 3A). Relative to a bare electrode or one modified with AuNPs, the resultant electrosensor was reported to exhibit excellent electrocatalytic activity when detecting INZ owing to a downward shift in its oxidation potential with the concomitant enhancement of its oxidation current. The authors were able to successfully utilize GCE/Au@PtNPs to measure INZ concentrations in samples of human blood and urine containing 100-fold higher concentration of theophylline (TP).

3.2. Carbon-reinforced metal nanocomposites

Carbon nanomaterials (CNs) exhibit robust physical and chemical properties that make them well-suited for use in electrochemical sensor development. Several CNs with distinct structural characteristics have been developed or leveraged in recent years in nanotechnological contexts, including fullerene, nanodiamonds, carbon dots (CDs), carbon nanotubes (CNTs), graphene (GR), and graphdiyne (GDY). These materials can also be grouped into 0-dimensional (0 D) nanodots, 1 D nanotubes, 2 D nanomaterials, and 3 D nanomaterials.[27,28] These CNs exhibit a basic structure consisting of sp^2-bonded carbon atoms,[29] and possess intrinsic properties that make them suitable for use in electrocatalyst design or as anchors to reinforce metallic catalyst components within developed sensors.[30–32] Hybridization of CNs and metal nanocatalysts have been the subject of significant interest owing to excellent electrical conductivity, combining the high electron mobility of CNs with the high charge carrier density of metals. Metal-carbon nanocomposites can facilitate more rapid electron transfer and support adsorption between analytes and the electrochemical interface, facilitating efficient redox reactions and augmenting the associated electrocatalytic reactions.[33,34] These properties result in the generation of electrochemical signals at low redox potential levels.[30] Using a nanocomposite composed of nitrogen-doped reduced graphene oxide (N-rGO), single-walled carbon nanotubes (SWCNTs), and PtNPs, Kong et al. successfully designed an electrochemical sensor capable of detecting the antitumor drug Daunorubicin (DNR)[35] (Figure 3B). The resultant N-rGO-SWCNTs-Pt nanocomposite exhibited excellent conductivity and a large surface area such that it was able to sensitively and quickly detect DNR in prepared samples of human serum.

3.3. Polymer-reinforced metal nanocomposites

Synthesizing and applying MNPs in a practical context is of key interest to the design of sensing platforms given the unique physicochemical properties of these materials. However, the widespread application of highly active MNPs continues to be hampered by their tendency to readily aggregate and associated stability limitations due to the high surface energy. As these nanoparticles undergo flocculation, their nano-scale size characteristics and associated properties are lost, thus reducing their electrocatalytic activity. In an effort to overcome this limitation, researchers have sought to embed MNPs into a variety of polymer-based matrices such that their electrocatalytic properties can be maintained through polymer-mediated stabilization and protection.[36,37] Moreover, the large polymer-metal interface that this approach necessitates can significantly affect polymer properties including crystallinity, conductivity, structural diversity, and free volume content.[38,39] A range of polymers has been employed in the development of polymer-reinforced metal nanocomposites, including both natural polymers such as alginate, gelatin, cellulose, and chitosan (CS), as well as synthetic polymers including polystyrene (PS), poly(glycolic acid) (PGA), poly(-lactic acid) (PLA), and polypyrrole (PPy).[40,41] These nanocomposites are generally synthesized from a mostly utilized subset of metals (Au, Pt, Pd, Ag, Cu, or Ti) and can be fabricated through approaches including, but not limited to, direct mixing, electrochemical synthesis, vapor-phase deposition, sol-gel processes, and *in situ* polymerization.[42,43] The appropriate selection of both polymers and metal components is critical to the design of an desired nanocomposite in this context, with the type of the polymer matrix as well as the size, quantity, and dispersion of the MNPs therein and interactions at the polymer-MNP interface all ultimately shaping the properties of the resultant nanocomposites.[39] Such polymer-reinforced metal nanocomposites have been widely utilized as electrode modifiers in the design of advanced electroanalytical sensors due to their advantageous electronic properties.[44] For example, an electrochemical sensor platform suitable for detecting an anthracycline antineoplastic drug Doxorubicin (DOX) was developed using a silver nanoparticles (AgNPs)-poly(chitosan)-modified GCE[45] (Figure 4A). When assessed via SWV and CV, the electrocatalytic properties of the resultant electrode were found to be conducive to the sensitive and selective detection of DOX in both lysates prepared from B16F10 cells and human bio-fluid samples. The results also revealed the remarkable electrochemical manners of electrodeposited AgNPs/CS nanocomposite may be due to the incremental connections within components through CS amine group, which hastens the flow of electrons between the electrode and analyte.

3.4. MOFs-reinforced metal nanocomposites

Metal-organic frameworks (MOFs) are porous crystalline materials composed of metal ions or ion clusters that are joined via coordination bonds with specific organic ligands. These MOFs are well-suited to use in a range of contexts owing to their high porosity, excellent catalytic activity, structural diversity, and large internal surface area.[46,47] As most pristine MOFs exhibit limited electrical conductivity and poor chemical stability in water, however, they are less feasible to utilize for electrochemical sensor in aqueous solutions.[48,49] Fortunately, these limitations can be overcome by combining MOFs with MNPs or other stable conductive materials.[50,51] Further, the highly tailorable pore environments in MOFs play a vital role in preventing the aggregation of MNPs, providing abundant active sites for catalysis and adsorption, and as such, a more tunable platform formed by integrating and dispersing MNPs into MOFs have attracted substantial research interest.[52,53] The presence of MOFs-reinforced metal nanocomposites on the electrode surface can enhance overall sensitivity and selectivity while minimizing interference, shifting analyte redox

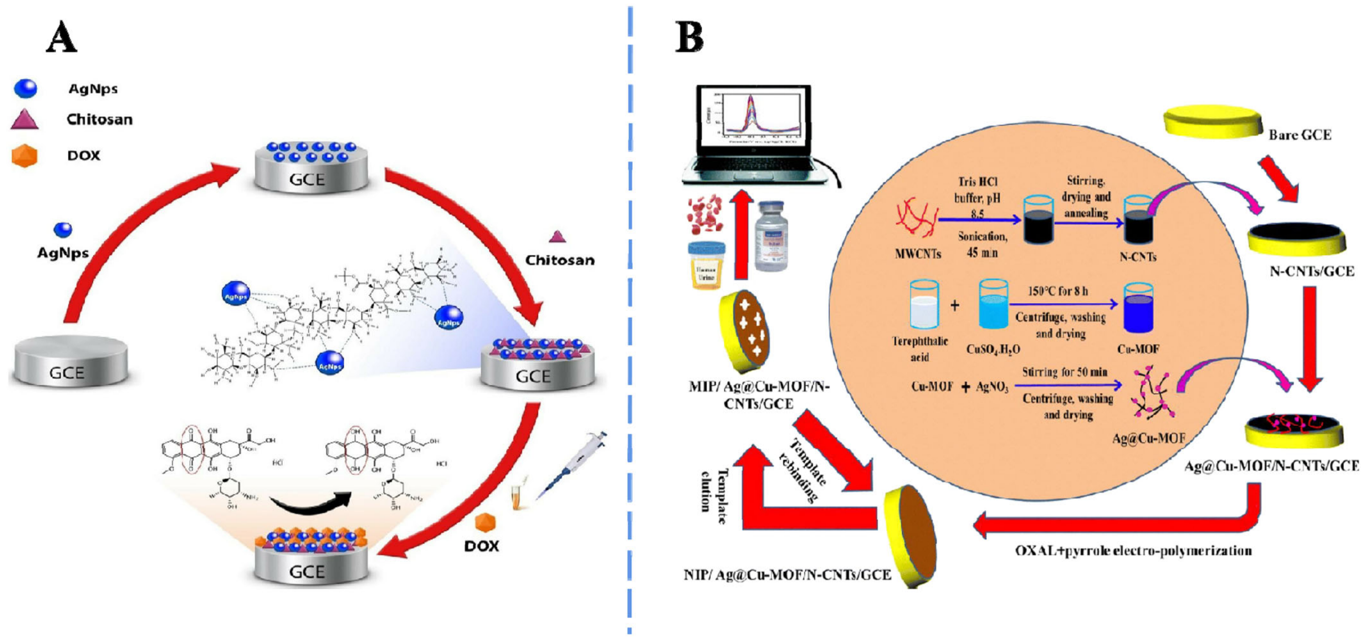

Figure 4. Schematic overview of (A) GCE/AgNPs/CS fabrication (Reproduced from Ref.,[45] with permission from Elsevier), and (B) MIP-Ag@Cu-BDC/N-CNTs/GCE preparation and OXAL detection (Reproduced from Ref.,[55] with permission from Springer).

potential to lower values in the context of electrochemical sensing.[54] In recent years, the use of MOF- and MNP-co-modified electrochemical (bio)sensors as tools for pharmaceutical analysis is a rapidly developing interdisciplinary research field. For example, Mahnashi et al. decorated a GCE surface with AgNP-functionalized Cu-MOF/Nitrogen-doped CNT (Ag@Cu-MOF/N-CNTs) nanohybrids to produce a selective and sensitive molecular imprinted polymeric network (MIP) electrochemical sensor capable of detecting the antineoplastic drug oxaliplatin (OXAL)[55](Figure 4B). The utilized nanohybrids simultaneously improved the electrocatalytic activity employed to detect OXAL while increasing the overall surface area available for the reaction. These MIP-based electrochemical sensors were successfully employed to detect this drug in samples of human urine and plasma, as well as in pharmaceutical injections, yielding good recovery and acceptable RSDs.

4. The use of electrochemical sensors and biosensors for pharmaceutical analysis

Owing to their advantageous properties, electrochemical (bio)sensors represent promising tools for the detection of pharmaceutical agents in a range of complex matrices. Here, we provide a comprehensive overview regarding the design of metal nanocomposite-based (bio)sensors that have been reported for the selective detection of drugs falling into six different categories: antibiotic, tuberculostatic, analgesic, antineoplastic, antipsychotic, and antihypertensive drugs.

4.1. Antibiotics

Antibiotics exhibit broad-spectrum antibacterial activity that is critical to the treatment of a range of infectious diseases. However, the excessive or inappropriate utilization of these antibiotics poses a major threat to public health and environmental integrity owing to their potential for food contamination, mutagenicity/carcinogenicity, and the potential for the development of multidrug-resistant bacteria.[56] It can be particularly dangerous in children, the elderly, and individuals suffering from organ insufficiency, underscoring the need to be able to reliably detect antibiotics in complex sample types. A range of electrochemical sensors have been developed and applied in the contexts of biological, pharmaceutical, and environmental sample analyses. Here, we discuss electrochemical (bio)sensors that have been designed to detect antibiotics including chloramphenicol (CAP), tetracycline (TC), amoxicillin (AMX), norfloxacin (NOR), and metronidazole (MTZ) (Table 1).

4.1.1. Chloramphenicol (CAP)

CAP is a broad-spectrum phenolic antibiotic that exhibits activity against both Gram-negative and Gram-positive bacteria and is often utilized to treat diseases in humans and animals. However, CAP can readily enter the human body when consumed in food or as a medicine, leading to the regulatory establishment of a maximum allowable dose.[57] The use of CAP in animal feed is now banned in the USA and China,[58] and it is thus critical that low-cost methods to sensitively and accurately detecting CAP be developed. Roushani et al. utilized AgNPs and (3-Aminopropyl) triethoxysilane-functionalized graphene oxide composite (AgNPs/[NH_2-Si]-f-GO) to design an electrochemical aptasensor for the selective detection of CAP[59]. Larger surface area and abundant amino groups in the synthesized nanocomposites provided an enhanced bioconjugation property with such biomolecules as DNA. In this platform, covalent aptamer (Apt) immobilization on a GCE surface was achieved through the use of AgNPs/[NH_2-Si]-f-GO layer, with a ferricyanide/ferrocyanide solution being utilized as an

Table 1. Selected applications for the analysis of antibiotic drugs by using metal nanocomposite-based electrochemical (bio)sensors (2017–2022).

S. No.	Pharmaceutical compound	Modified metal nanocomposite	Electrode	Electroanalytical method	Linear range	LOD	Real sample	Ref.
1	CAP	Apt/AgNPs/[NH_2–Si]-f-GO	GCE	DPV	10 pM–0.2 μM	3.3 pM	Milk, honey	[59]
2		Apt/PEI-rGO/AuNCs	AuE	DPV	5 pM–1 μM	2.08 pM	Chicken	[60]
3		CNTs/AgNWs	GCE	CV, DPV	0.1–100 μM	0.08 μM	Water	[61]
4		rGO–NHS–AuNFs	SPE	DPV	0.05–100 μM	1 nM	Blood serum, poultry feed, milk, eggs, honey, powdered milk	[62]
5		rGO/PdNPs	GCE	DPV	50–1000 nM	50 nM	Tap water, honey	[76]
6		PdNPs/GO	GCE	Amperometry	0.007–102.68 μM	1 nM	Milk, urine	[77]
7		AuNPs/C_3N_4/GN	GCE	SWV	0.7–120 μM	27 nM	Milk	[78]
8		Apt/rGO/AgNPs	GCE	LSV	0.01–35 μM	2 nM	Milk	[79]
9		Cu–BCN	GCE	DPV	0.01–12 μM	2.41 nM	Tap water, lake water	[80]
10		rGO@PDA@AuNPs	GCE	DPV	0.1–100 μM	0.058 μM	Milk	[81]
11	TC	Au/g-C_3N_4	GCE	CV	0.1–20 μM 20–200 μM	0.03 μM	Tablet	[63]
12		apta-CNQD@AgNPs	AuE	DPV	1 nM–0.1 mM	0.26 nM	Milk	[64]
13		ErGO/Cu-MOF/PtNPs	GCE	Amperometry	1–200 μM	0.03 μM	Tap water, lake water	[65]
14		Ag/GO	BDDE	Amperometry, DPV, SWV, MPA	–	0.005 μM	Surface water	[82]
15		Apt/MNPs/AuNPs	PGE	EIS	1.0 pM–1.0 μM	0.03 pM	Milk	[83]
16		Zr-UiO-66/MWCNTs/AuNPs	GCE	Amperometry	0.5 μM–0.225 mM	0.167 μM	Lake water	[84]
17		MIOPPy-AuNPs	SPCE	DPV	1–20 μM	0.65 μM	Shrimp	[85]
18	AMX	MIP-RGO/OPPy/AuNPs	GCE	CV	1–1000 μM	1.22 μM	Milk, serum	[66]
19		Gr/AuNPs/Lac	GCE	Amperometry	0.425–292 μM	0.425 μM	–	[67]
20		Apt/TiO_2-g-C_3N_4@AuNPs	GCE	EIS	0.5–3 nM	0.2 nM	Actual wastewater	[68]
21		TiO_2/CMK-3/AuNPs/Nafion	GE	CV	0.5–2.5 μM 2.5–133 μM	0.3 μM	Mineral water, environmental water , antibiotic capsule	[86]
22	NOR	PAMAM-Au	GCE	DPV	1–1×10^5 µg·L^{-1}	0.3837 µg/L	Milk, egg, pork	[69]
23		PAA/CoNPs	SPCE	SWV, EIS	–1–5×10^{-4} M	0.979 mM 0.228 mM	–	[70]
24		MIP/CoFe-MOFs/AuNPs	GCE	DPV	5–100 pM 100–1000 pM 1000–6000 pM	0.131 pM	Capsule, milk	[71]
25		MWCNT-CPE/pRGO-ANSA/Au	CPE	DPV	0.03–1.0 μM 1.0–50.0 μM	0.016 μM	Capsule, rat plasma	[87]
26		MIP/BPNS-AuNP	GCE	LSV	0.1 nM–10 μM	0.012 nM	Milk, tap water, soil	[88]
27	MTZ	AuNP@PDDA/GH	GCE	LSV	0.4–656.4 μM	0.097 μM	Tablet	[73]
28		GO@AgNPs	GCE	Amperometry	0.09 μM–4.594 mM	69 nM	Flagyl	[74]
29		AgNP/CuMOF/PPy–rGO	CPE	ASSWV	0.08–160 μM	24 nM	Tablet, urine	[75]
30		MWCNTs/CTS-Ni	GCE	DPV	0.1–150 μM	0.025 μM	Tablet, serum , urine	[89]
31		Pt nanospheres/polyfurfural film	GCE	DPV	2.5–500 μM	50 nM	Serum	[90]
32	Furazolidone (FZD)	Pt–Re NP/PAC	GCE	LSV, DPV	1.0–299 μM 0.2–117.7 μM	75.5 nM 20.8 nM	Serum, urine	[91]
33		Gr/Au	GCE	Amperometry, DPSV	1–674 μM 0.02–400 μM	0.64 μM 0.0126 μM	Pork	[92]

C_3N_4: carbon nitride; PdNPs: palladium nanoparticles; MNPs: magnetic nanoparticles; MIOPPy: molecularly imprinted overoxidized polypyrrole; CMK-3: CMK-3-type mesoporous carbon; pRGO: partially reduced graphene oxide; ANSA: 6-aminonaphthalene-2-sulfonic acid; BPNS: black phosphorus nanosheet; CTS-Ni: chitosan-nickel; PAC: porous activated carbon.

electrochemical probe. Based on the property that the formation of CAP-Apt complex on the electrode surface increased the electron transfer resistance, in the presence of CAP, the peak current decrease of the redox probe can be obtained. CAP measurements with this system were made via DPV in a wide linear concentration range, achieving a low limit of detection (LOD) and detecting CAP effectively in real samples.

Lu and coworkers similarly synthesized an electrochemical aptasensor designed to detect CAP via the immobilization of ssDNA-binding proteins on a composite matrix of polyethyleneimine-functionalized reduced graphene oxide and gold nanocubes (PEI-rGO/AuNCs).[60] In this study, PEI was used to prevent rGO agglomeration and to improve its stability. Moreover, AuNCs uniformly dispersed on the surface of PEI-rGO have higher surface energy and more available reaction sites than AuNPs, indicating that more CAP-binding aptamers can be immobilized via Au-S affinity. The resultant nanocomposites exhibited excellent electrical conductivity and a high surface-to-volume ratio well-suited to signal amplification. Thus, the prepared sensor accurately detected CAP that had been spiked into samples of chicken. Zhu et al., in contrast, fabricated a CAP sensor using CNTs and Ag nanowire composites (CNTs/AgNWs),[61] with both of these components contributing to CAP redox reaction dynamics. AgNWs additionally exhibited thermodynamic advantages. CV and DPV testing revealed the prepared sensor to exhibit a satisfactory performance. This sensor also exhibited practical utility as evidenced by its selectivity and repeatability. In a separate report, Ali et al. utilized nanocomposites composed of N-hydroxysuccinimide (NHS)-crosslinked rGO sheets that had been functionalized using gold nanoflowers (AuNFs).[62] A modified screen-printed electrode (SPE) modified with these rGO-NHS-AuNFs was able to sensitively and selectively detect CAP even in various real samples. The obtained results show that AuNFs successfully prevented rGO sheet aggregation and augmented overall electrochemical performance.

4.1.2. Tetracycline (TC)

Since initially being discovered in the 1950s, the polyketide antibiotic TC has been widely used to treat various bacterial infections. Several electrochemical sensors have been reported as tools for quantitatively detecting TC within a variety of foods, biological samples, and environmental contexts. For example, Guo et al. employed a one-step pyrolyzation strategy to synthesize AuNPs on the surface of graphitic carbon nitride (g-C_3N_4), yielding Au/g-C_3N_4 nanocomposites exhibiting promising electrocatalytic activity for TC oxidation relative to either component material alone.[63] The morphological analysis confirmed abundant AuNPs with no agglomeration were homogeneously anchored onto the surface of g-C_3N_4, owing to larger surface area and more active sites of g-C_3N_4. The porous heterostructure of Au/g-C_3N_4 nanocomposite further leaded to stepped-up mass and electron transfer. Hence, CV measurements using this sensor exhibited reproducible and stable operability. Separately, researchers designed a nanocomposite consisting of aptamer-based carbon nitride quantum dot and AgNPs (apta-CNQD@AgNPs), with the resultant nanoprobe having been successfully leveraged for the fluorometric and electrochemical dual-mode detection of TC[64]. The prepared apta-CNQD@AgNPs selectively and sensitively detected TC within samples of milk that had been spiked with this antibiotic. Electrochemical experiments showed the hybrid of CNQD by AgNPs can address the shortcomings of CNQDs and therefore improve the fluorometric and electrochemical performance at the same time. In yet another report, Xu et al. modified a GCE with the electrochemically reduced GO, Cubased MOF and PtNPs, yielding an ErGO/Cu-MOF/PtNPs composite electrode capable of detecting TC in the tap water and lake samples.[65] With better anti-interference performance, this promising sensing platform could be performed to determine analogous or total TC antibiotics for actual application.

4.1.3. Amoxicillin (AMX)

The β-lactam antibiotic AMX exhibits low biodegradation rates, robust chemical stability, and high levels of toxicity. Multiple recent reports have described the design of sensitive and efficient detectors for AMX using a series of different nanocomposites. In one report, for example, AuNPs and rGO were combined with a molecular imprinted overoxidized polypyrrole (MIOPPy) film exhibiting excellent cationic changes, enabling the sensitive, selective, stable, and efficient detection of AMX using the resultant molecularly imprinted sensor.[66] The developed nanocomposite membrane was characterized by scanning electron microscopy (SEM), UV-Visible, Fourier transform infrared spectroscopy (FTIR) and some experimental parameters were also optimized. Based on properties of a sensitive 2D Gr/AuNP nanocomposite and laccase (Lac), an electrochemical biosensor was developed for the analysis of AMX by Osikoya's group.[67] The use of Lac with AuNPs serving to boost electrocatalytic current responses was demonstrated through EIS and CV characterization. Aptamer-based sensors have also been reported as tools for detecting AMX over the last two years, taking advantage of the robust secondary structural characteristics of aptamers to enable reassembly when ligands are not present such that a blank signal is produced. Song et al. developed one such ultrasensitive impedimetric aptasensor through synergistic interactions between AuNPs and TiO_2-g-C_3N_4, with the formation of an Au-S bond between AuNPs and the thiol-aptamer therein enabling the specific recognition of AMX on a modified GCE surface, resulting in a corresponding and rapid increase in the associated impedance signal.[68]

4.1.4. Norfloxacin (NOR)

As a second-generation fluoroquinolone antibiotic, NOR has been widely used to treat bacterial infections for over five decades. As it degrades slowly, however, NOR is present in many water sources. In an effort to detect NOR in animal-derived foods, one research team designed an electrochemical immunosensor consisting of a poly (amidoamine)

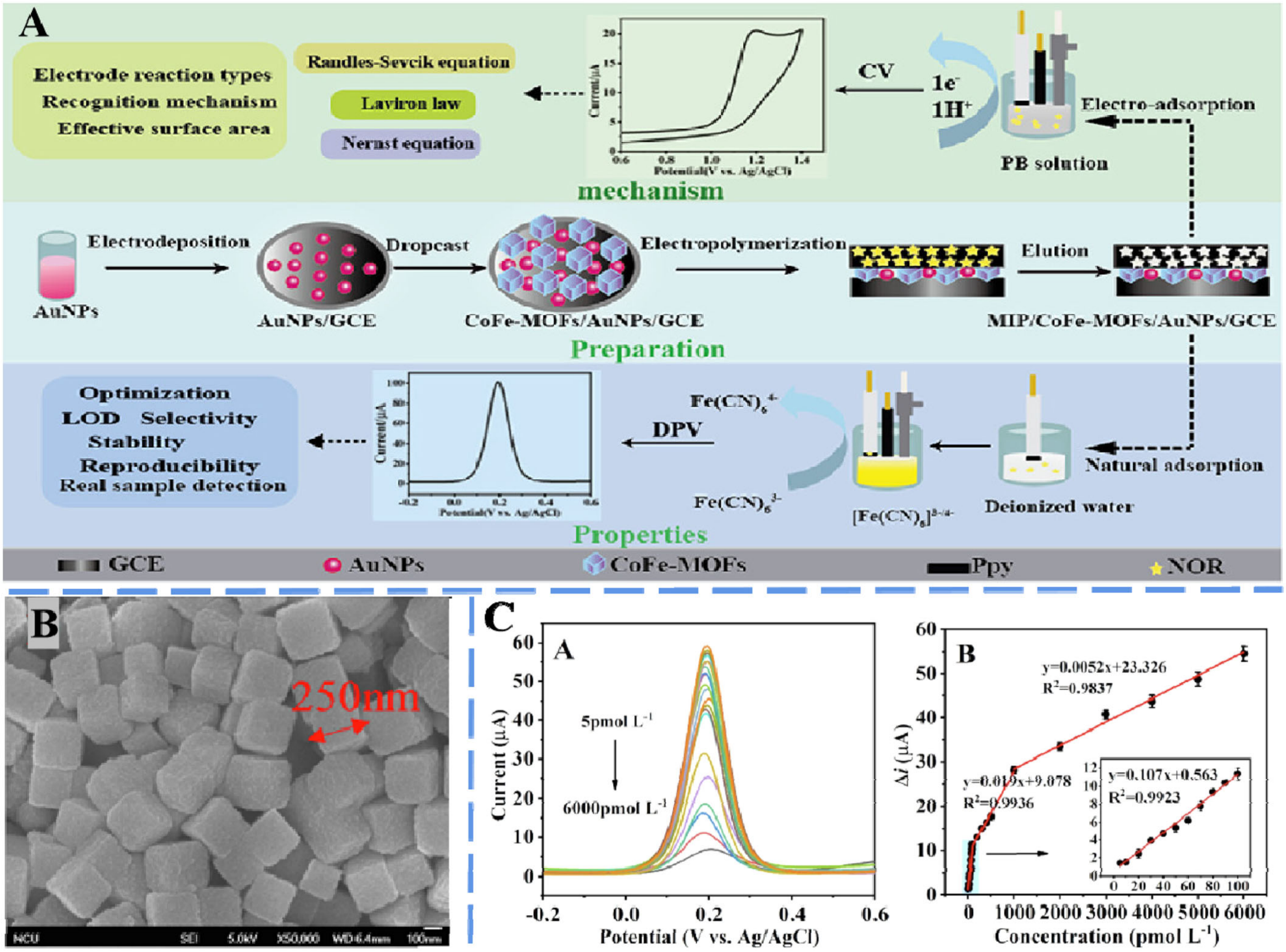

Figure 5. (A) The preparation, properties and mechanism determination process of the indicated sensor; (B) SEM images of MIP/CoFe-MOFs/AuNPs; (C) DPV-based quantitative NOR detection (Reproduced from Ref.,[71] with permission from Elsevier).

dendrimer-encapsulated AuNP composite (PAMAM-Au), yielding a large surface area and high conductivity ideal for appropriate antibody loading and specific NOR detection.[69] Another separate research team leveraged CoNPs and their synergistic interactions with polyamic acid (PAA) on screen-printed carbon electrodes (SPCEs) to directly detect NOR via an electrochemical approach.[70] In this platform, the PAA/CoNPs-modified electrode shifted the NOR oxidation potential while improving overall electrode stability. Recently, Ye et al. designed a novel polypyrrole (Ppy)-based molecularly imprinted electrochemical sensor combining AuNPs and 3 D CoFe-MOFs.[71] The prepared AuNPs and CoFe-MOFs were successively modified on the surface of GCE by electrodeposition and physical absorption. Last step was to self-assembly electropolymerize MIP membrane onto the modified electrode. Figure 5A shows the preparation, properties and mechanism determination process of the MIP/CoFe-MOFs/AuNPs/GCE sensor for NOR. MIP/CoFe-MOFs/AuNPs exhibited as a regular nano cube with a uniform size and a rough surface with the side length of about 250 nm (Figure 5B). Researchers have made an effort to increase the effective surface area of the imprinted cavities capable of identifying NOR by using nanocomposites, thus contributing to improving the performance of electrochemical sensor. Under optimal conditions, DPV-based analyses conducted using this sensor were able to detect NOR quantitatively (Figure 5C).

4.1.5. Metronidazole (MTZ)

MTZ (2-methyl-5-nitroimidazole-1-ethanol) is a nitroimidazole derivative with robust antimicrobial activity. It can also be readily detected using a range of electrochemical sensor platforms, as the aromatic nitro group therein can be readily reduced in a range of contexts.[72] For example, Veerakumar et al. reported AuNP-decorated poly(diallyldimethylammonium chloride) (PDDA) functionalized graphene hydrogel (AuNP@PDDA/GH) nanocomposites were synthesized by a simple hydrothermal method and used for fabricating a MTZ sensor.[73] Firstly, GO sheets were prepared from graphite powders by Hummers' method with slight modification. In the second step, GO, PDDA and $HAuCl_4$ were mixed with ultrasonic treatment, and then freeze-dried after HT treatment to synthesize AuNP@PDDA/GH composites. Finally, dispersed AuNP@PDDA/GH electrocatalyst was drop-casted on the pre-cleaned GCE surface and dried at 50 °C for 30 min. Figure 6A shows the preparation procedure of the AuNP@PDDA/GH composites in details.

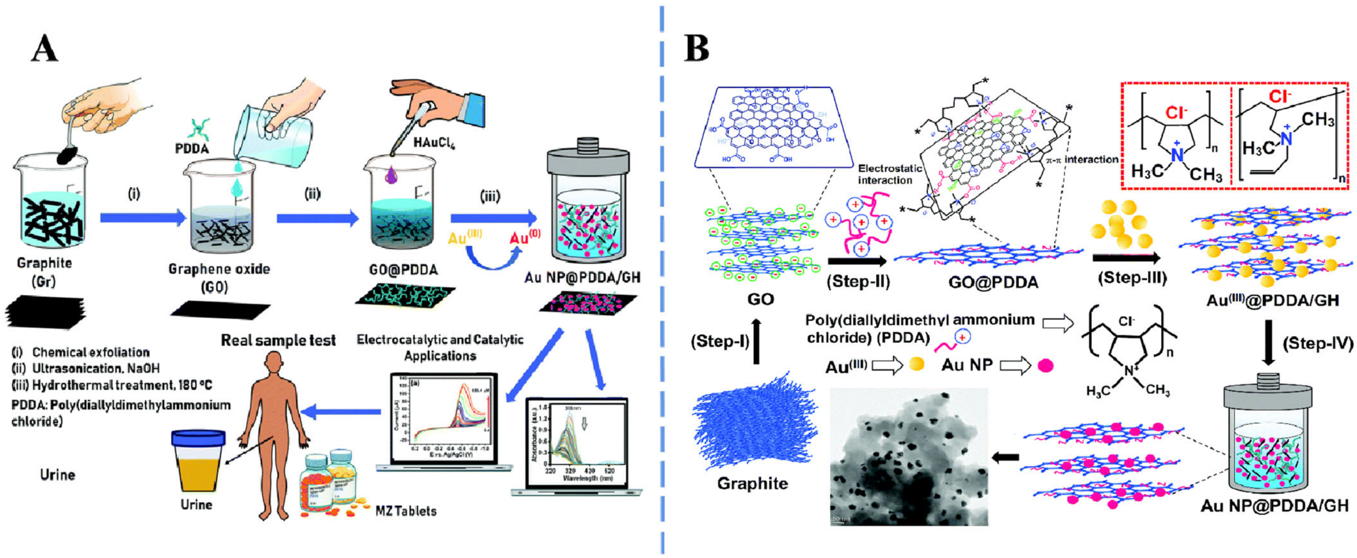

Figure 6. Schematic overview of (A) MTZ sensor preparation and measurement processes; (B) Au NP@PDDA/GH composite preparation (Reproduced from Ref.,[73] with permission from The Royal Society of Chemistry).

According to the characterization analysis, the well-dispersed AuNPs were evenly decorated on the GO surface by means of water-soluble cationic polyelectrolyte PDDA, as illustrated in Figure 6B, forming a new hierarchical nanostructure in favor of electron transfer and further catalytic efficiency. The resultant sensor benefited from synergistic catalytic properties associated with its constituent components, achieving selective and sensitive MTZ detection. In a separate report, researchers employed an eco-friendly one-pot approach with a *Goniothalamus wightii* biomass-derived solution to prepare GO@AgNPs nanocomposites for electrochemical MTZ detection, successfully identifying this drug in preparations of Flagyl (500 mg) with satisfactory recovery results.[74] Considering the potential application of MOF, Saedi and coauthors further combined PPy hemispherical molecule-coated reduced graphene oxide (PPy-rGO) and CuMOF to increase the number of active catalytic sites available for rapid electron transfer.[75] Subsequently, the synthesized nanocomposite was functionalized with AgNPs through *in situ* silver ion reduction. In this study, ASSWV was employed to assess AgNP/CuMOF/PPy-rGO/CPE sensor electrocatalytic activity in the context of MTZ reduction, yielding greater sensitivity and analytical signal strength than that observed for CV.

4.2. Tuberculostatic drugs

Tuberculosis (TB) is among the 10 leading causes of global human mortality, affecting an estimated 10 million persons annually. The most commonly prescribed medications for patients with TB include INZ as well as ethambutol (EBL), rifampicin (RIF), and pyrazinamide (PZA), all of which are included on the WHO essential medicines list.[93] The routine intake of these tuberculostatic agents or an overdose can result in hepatotoxicity, liver damage, and potentially death. It is thus critical that inexpensive, reliable, and straightforward approaches to detecting these drugs be developed, spurring extensive research in the pharmaceutical field. Table 2 shows the wide application of metal nanocomposite-based electrochemical (bio)sensors in the analysis of tuberculostatic drugs.

4.2.1. Isoniazid (INZ)

INZ (pyridine-4-carboxylic acid hydrazide) exhibits sterilizing potential, leading to its being the most commonly employed first-line therapy for TB patients. Several electrochemical approaches to detecting and measuring INZ have been reported to date. For example, Nellaiappan et al. employed AuNP-decorated CNFs with a chitosan-modified carbon screen-printed electrode (Au_{nano}@CNF-CHIT/SPE) to develop an electrochemical sensor for flow injection-based analyses of INZ at neutral pH[94]. The chitosan contains many functional groups like -OH and $-NH_2$, making it superb to form the polysaccharide films on the surface of CNFs. It is noteworthy that solution pH alterations affect the catalytic behavior of INZ due to the immediate impact of the chitosan functional group toward AuNPs formation. Hence, in pH 7 optimal buffer solution, the authors were able to detect INZ in pharmaceutical formulations with a good recovery rate ($100 \pm 5\%$), underscoring the simplicity and viability of this approach. In another study, researchers reported the application of an electrochemical sensor constructed based upon the electrochemical deposition of Cu microparticles on a GO nanosheet-modified GCE (Cu/GO/GCE) and explored its utility as a tool for quantitatively measuring INZ concentrations in biofluids.[95] Synergistic interactions between GO and Cu markedly enhanced INZ electrochemical responses for this sensor platform, enabling the analytical detection of INZ with a broad linear range and a low LOD while retaining excellent selectivity and stability. Likewise, Zareie et al. further reported the design of a ternary nanocomposite GO/gold nanourchin (GNU)/MIP assembled on SPCE capable of detecting INZ even in the presence of anionic species from these families of drugs.[96] The readily-synthesized GO/GNU nanocomposites provided

Table 2. Selected applications for the analysis of tuberculostatic drugs by using metal nanocomposite-based electrochemical (bio)sensors (2017–2022).

S. No.	Pharmaceutical compound	Modified Metal nanocomposite	Electrode	Electroanalytical method	Linear range	LOD	Real sample	Ref.
1	INZ	Au_{nano}@CNF-CHIT	SPE	FIA	1 μM–1 mM	0.172 μM	Tablet	[94]
2		Cu/GO	GCE	Amperometry	0.15–500 μM	23.4 nM	Serum, urine	[95]
3		MIP/GNU/GO	SPCE	DPV	2.5–850 nM	0.85 nM	Serum, urine	[96]
4		Ag–gC_3N_4–rGO	CPE	SWV	0.8–70 μM	0.2 μM	Tablet, urine	[102]
5		PANSA/PVP-AgNPs	AuE	DPV	2–22 μM	0.65 μM	Serum, urine	[103]
6		Ag-P(MMA-*co*-AMPS)	GCE	Amperometry	50 nM–150 μM	10 nM	Tablet	[104]
7	RIF	PMel-Au_{nano}	GCE	LSV	0.08–15.00 μM	0.03 μM	Urine	[97]
8		AgNPs/3D rGO	GCE	DPV	0.01 nM–45 μM	0.81 nM	Human blood	[98]
9		Au/VXC72R-chitosan	GCE	Amperometry	0.5–10 μM	0.11 μM	Bovine serum	[105]
10	PZA	AgND/LDH	GCE	DPV	0.9–250 μM	0.72 μM	Serum, urine	[99]
11		GO/AgNPs/CYP2D6	GCE	CV	100–600 μM	0.0029 nM	–	[100]
12		Ionic liquid-reduced graphene oxide-AgNPs	GCE	DPV	3–24 μM	0.0102 μM	Tablet	[101]
13	Ethambutol (EBL)	P_{Mel}-Au_{nano}	GCE	DPV	0.5–150 μM	0.21 μM	Urine	[106]

PANSA: poly(8-anilino-1-naphthalene sulfonic acid; PVP: polyvinylpyrrolidone; P(MMA-*co*-AMPS): methyl methacrylate and 2-acrylamido-2-methylpropane sulfonic acid; P_{Mel}: poly-melamine.

an effective support framework, increasing the surface area to accelerate electron transfer and amplify overall performance, yielding the practical application of the proposed sensor for measuring INZ in real samples such as blood serum and urine.

4.2.2. Rifampicin (RIF)

Multiple research groups have reported on the development of electrochemical sensors used in the context of RIF detection and analysis. For example, Amidi et al. employed AuNPs deposited onto an electropolymerized poly-melamine-modified pre-anodized GCE surface (PMel-Au_{nano}/GCE),[97] thereby producing a sensor with markedly enhanced oxidation responses to RIF with significant ~0.10 V decreases in peak overpotentials owing to the synergistic properties of the constituent component. This sensor was able to detect RIF effectively when performing voltammetric measurements. A separate research group employed an AgNPs/3D rGO nanocomposite to detect RIF with a DPV sensor that benefited from the synergistic interplay to yield more robust catalytic activity and conductivity such that RIF oxidation could be reliably detected on the electrode surface.[98] This sensor similarly yielded good sensitivity, an acceptable linear detection range, and a low LOD without any interfering substances, making it well-suited to the analysis of real-world samples.

4.2.3. Pyrazinamide (PZA)

PZA, which is sometimes referred to as pyrazinecarboxamide, is an artificial nicotinamide pyrazine analog with robust anti-TB activity that is commonly deployed in combination with EBL or other drugs to decrease the TB treatment course from 9 months to 6 months. As PZA treatment over extended periods can result in significant side effects, there has been substantial interest in the development of metal nanocomposite-based electrochemical sensors capable of detecting this drug. Amini et al. designed a sensitive electrochemical sensor for PZA using Ag nanodendrites (AgNDs) that were electrodeposited onto an electrode that had undergone Zn-Al layered double hydroxide (LDH) modification.[99] The resultant sensor exhibited novel surface structural characteristics attributed to the interface between AgNDs and LDH and the high associated surface area, enabling stable PZA detection with good stability over a two-week period. Separately, AjayI et al. fabricated a GO/AgNP nanocomposite-modified cytochrome P450-2D6-based electrochemical biosensor for PZA using a synthetic process that relied in part upon pear extract.[100] Their resultant sensor was able to quantitatively detect this drug at a LOD below the peak concentrations thereof observed in human plasma samples, making it an effective, inexpensive, and sensitive biosensor well-suited to detecting PZA. In another recent study, researchers utilized AgNPs, 1-ethyl-3-methylimidazolium tetrafluoroborate ([Emim][BF_4]) ionic liquid, and rGO to prepare a nanocomposite-based electrochemical sensor.[101] To our knowledge, ionic liquids (ILs) have infrequently been reported as cross-linkers for electrode construction and modification because of their basic properties such as high electrical conductivity and wide electrochemical window. By covalent binding with IL, the synthesized AgNPs with an average size of ~30 nm were homogeneously dispersed on the outer layer of the rGO. The incorporation of the IL significantly improve the electrooxidation catalytic effect for PZA, and the resultant sensor was shown to reliably quantify levels of PZA in pharmaceutical tablets.

4.3. Analgesic drugs

Analgesic drugs are the most widely utilized over-the-counter (OTC) agents employed in the world, being employed to treat diverse conditions such as postoperative pain, osteoarthritis, and rheumatoid arthritis. These analgesics include both opioid and non-opioid medications, the latter of which consist of acetaminophen (AP) and non-steroidal anti-inflammatory drugs (NSAIDs), which are further subdivided into traditional NSAIDs and selective cyclooxygenase (COX)-2 inhibitors.[107] While safe when used appropriately, these analgesic drugs can result in toxicity stemming from abuse, acute overdose, or use in combination with certain other pharmaceuticals. In addition, the inappropriate disposal of these drugs can pose a significant environmental

Table 3. Selected applications for the analysis of analgesic drugs by using metal nanocomposite-based electrochemical (bio)sensors (2017–2022).

S. No.	Pharmaceutical compound	Modified metal nanocomposite	Electrode	Electroanalytical method	Linear range	LOD	Real sample	Ref.
1	AP	Pd-MWCNTs	GCE	DPV	0.5–100 μM	0.13 μM	Commercial drug	[108]
2		Ag-ZIF-67p	GCE	DPV	0.5–200 μM	0.2 μM	Tablet	[109]
3		(Au/Ag/Pd) NPs/EPGrO	GCE	DPV	5–700 μM	0.12 μM	Serum	[110]
4		mpg-CN/BP-Au	GCE	DPV	0.3–120 μM	0.0425 μM	Tablet	[111]
5		Pd/PSi	CCILE	DPV	0.3–15 μM	24 nM	Tablet, serum	[124]
6		Ni/NiO/Ni–B/Gr	GCE	Amperometry	10–2500 μM	14 μM	Tablet	[125]
7		AuNP/NCNO	GCE	DPV	25 nM–35 μM	9 nM	Tablet, serum	[126]
8		RuNPs/CTGONS	GCE	SWV	10–120 μM	0.023 μM	Serum	[127]
9		GO/Fe_3O_4/PMDA/Pd	GCE	DPV	5 nM–2.5 μM	2.1 nM	Serum	[128]
10		MWCNT/ZnO/Au	GCE	SWV	0.05–20 μM	9 nM	Tablet	[129]
11		AuNPs@TC8A/GN	GCE	DPV	0.5–120 μM	0.1 μM	Tablet	[130]
12		Au/NPCs	GCE	DPV	0.12–95.10 μM	49.4 nM	Pharmaceutical samples	[131]
13		TC8A/AuNPs/MWCNTs	GCE	DPV	1–150 μM	0.2 μM	Tablet	[132]
14		AgNPs-CB-PEDOT:PSS	GCE	SWV	0.62–7.1 μM	12 nM	Synthetic urine, river water	[133]
15		Au/Pd/rGO	GCE	DPV	1–250 μM	0.3 μM	Tablet	[134]
16		PEDOT/AG	GCE	Amperometry	0.15 μM–5.88 mM	41 nM	Medicament	[135]
17		Au/ZIF-L	GCE	DPV	3.50 μM–0.056 mM	1.02 μM	Tablet	[136]
18		Au/POM/NHCS	GCE	Amperometry, DPV	0.02–4.74 μM	4.56 nM	Pharmaceutical samples	[137]
19		Au@Fe-MOF	GCE	DPV	0.5–18 μM	0.12 μM	Urine, paracetamol	[138]
20		Pt/OMC	GCE	DPV	0.07–33.8 μM	0.015 μM	Pharmaceutical samples	[139]
21	DIC	f-MWCNTs-GO/AuNPs	AuE	DPV	0.4–80 μM 100–1000 μM	0.09 μM	Water, tablet, urine	[112]
22		Au–PtNPs/f-MWCNTs	AuE	DPV	0.5–1000 μM	0.3 μM	Tablet, urine	[113]
23		PtNFs/rGO	SPE	DPV	0.1–100 μM	0.04 μM	Urine	[114]
24		NiNPs/ERGO	GCE	SWV	0.25–125 μM	0.09 μM	Tablet, urine	[140]
25	ASA	polypyrrole/sol-gel/ SiO_2@AuNPs MIP	AuE	SWV	1.0–10.0 nM 10.0–100.0 nM	0.2 nM	Tablet, urine	[115]
26		Cs + AuNPs	SPCE	DPV, EIS	1 pg/mL–1 μg/mL	0.03 pg/mL	Urine	[116]
27		tPANI-Au@Pt-MWCNT	GCE	DPV	5.0–375.0 μM	2.0 μM	Tablet	[117]
28	TRA	f-MWCNTs/AuNPs	PGE	DPV	0.012–0.1 μM 0.1–3 μM	0.005 μM	Tablet, urine	[118]
29		Pt-NiO/MWCNTs	GCE	DPV	1.0–240 μM	0.084 μM	Serum, urine	[119]
30		(PANI-AgNPs)/MIP	Au-SPE	DPV, EIS	0.01–100 μg/mL	9.42 μg/mL	Urine	[120]
31		HTP–AuNPs/GN	CPE	DPV	1.0–100.0 μM	0.82 μM	Tablet, urine	[141]
32	PIR	ZnO–Pd/CNT	GCE	DPV	0.1–90 μM	0.04 μM	Serum, urine	[121]
33		Pt-N-rGO-SWCNTs	GCE	DPV	0.06–60 μM	0.015 μM	Tablet	[122]
34		Pt-NiO/MWCNTs	GCE	DPV	0.6–320.0 μM	0.061 μM	Serum, urine	[123]
35		AgNPs-SWCNTs-rGO	GCE	LSV, Amperometry	1–100 μM 0.05–250 μM	0.5 μM 0.5 nM	Tablet	[142]
36	Naproxen (NAP)	CNF/Au/PANI	CPE	DPV	0.05–20 nM	0.016 nM	Capsule, urine	[143]
37		AgNPs@GO-β-CD	G-DVD	DPV	0.4–80 μM	0.023 μM	Tablet, urine	[144]

PSi: porous silicon; Ni-B: nickel-boron; EPGrO: electro-pretreated graphene oxide; NCNO: nitrogen-doped carbon nano-onions; CTGONS: chemically treated graphene oxide nanosheets; PMDA: poly-methyldopa; TC8A: thiolated calix[8] arene; NPCs: nanostructured porous carbon; ZIF-L: leaf-like zeolitic imidazolate framework; POM: polyoxometalate; NHCS: nitrogen-doped hollow carbon sphere; OMC: ordered mesoporous carbon; HTP: 4-hydroxyl-2-(triphenylphosphonio)phenolate; β-CD: β-cyclodextrin.

hazard. To date, however, relatively few electrochemical sensors have been designed to detect analgesic drugs (Table 3).

4.3.1. Acetaminophen (AP)

AP, also referred to as paracetamol, has long been employed as an antipyretic and analgesic drug with limited anti-inflammatory efficacy. AP overdoses, however, can cause severe damage to the skin, pancreas, and liver, potentially resulting in death. Wu and coworkers employed a DPV approach together with a Pd and multi-walled CNT nanocomposite (Pd-MWCNTs)-modified GCE to analyze AP electro-oxidative responses (Figure 7A), with the Multiwfn and Gaussian 09 methods being employed in computer simulations to further explore the redox mechanism of AP[108]. The resultant sensor was able to quantitatively detect AP with a wide linear response range and a low LOD. Prolonged AP use *in vivo* has been reported to decrease dopamine (DA) levels, with AP thereby being capable of protecting against stress-related damage caused by elevated DA concentrations, further underscoring the value of detecting DA and AP in biological and pharmacological contexts. In a separate report, researchers utilized AgNPs fabricated on a GCE via the ultrasonication and reduction of precursor $AgNO_3$ together with 3 D porous Co-based MOFs known as ZIF-67 nanopinnas to prepare an Ag-ZIF-67p composite[109] (Figure 7B). The resultant sensor exhibited enhanced electrocatalytic activity for AP and DA owing

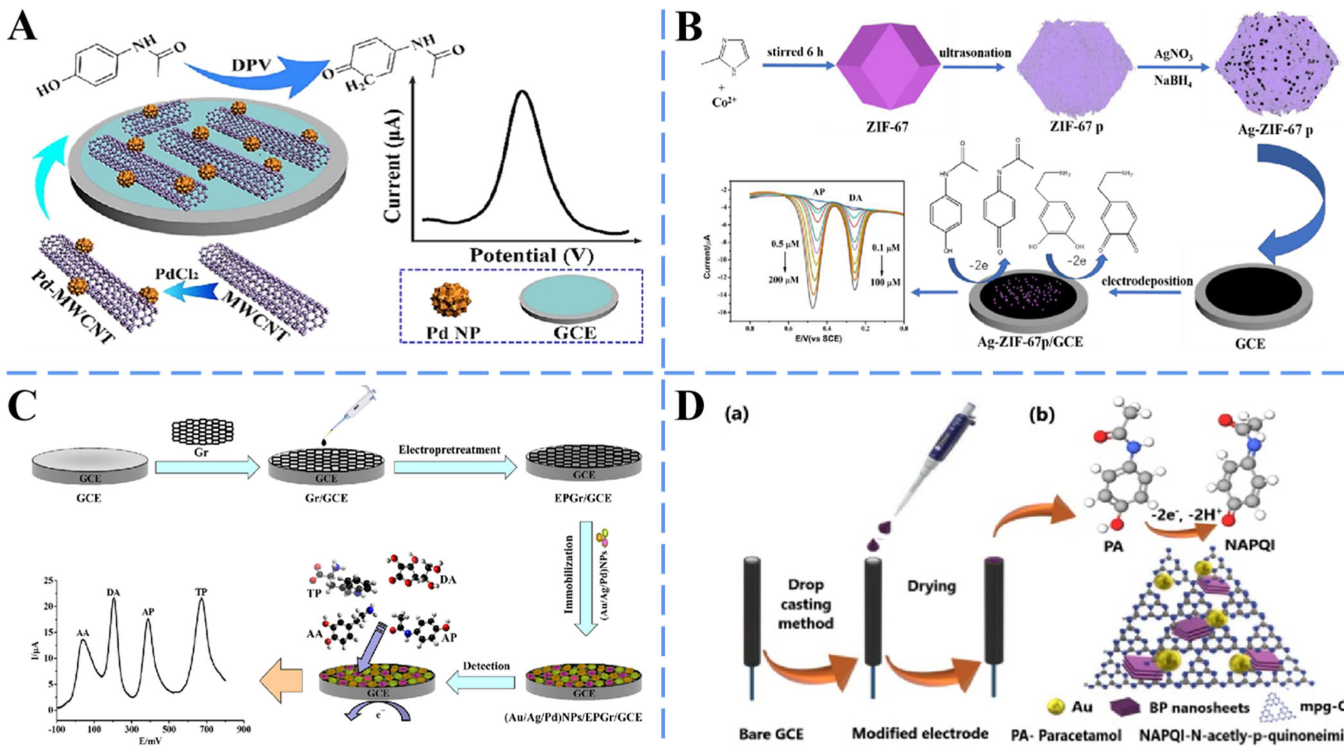

Figure 7. Schematic overview of (A) Pd-MWCNTs/GCE preparation for AP detection (Reproduced from Ref.,[108] with permission from Elsevier); (B) Ag-ZIF-67 nanopinnas-modified GCE fabrication and use to detect AP and DA (Reproduced from Ref.,[109] with permission from Elsevier); (C) stepwise (Au/Ag/Pd)NPs/EPGrO nanocomposite sensor preparation and AA, DA, AP, and TP electrocatalytic pathways (Reproduced from Ref.,[110] with permission from Elsevier); (D) drop casting-based modified electrode preparation and AP oxidation mechanisms (Reproduced from Ref.,[111] with permission from Elsevier).

to the high conductivity and catalytic activity of the utilized AgNPs together with the porosity and high surface area of ZIF-67. In another published work (Figure 7C), Abdelwahab et al. further employed (Au/Ag/Pd) NPs/EPGrO nanocomposites to facilitate the simultaneous voltammetric detection of ascorbic acid (AA), DA, AP, and tryptophan (TP) in human serum samples.[110] Yanalak et al. utilize AuNPs, mesoporous graphitic carbon nitride, and black phosphorus to prepare a ternary mpg-CN/BP-Au nanocomposite to facilitate photocatalytic hydrogen evolution and electrochemical AP detection (Figure 7D), yielding a linear detection range of 0.3–120 μM and a 0.0425 μM LOD consistent with improved performance.[111]

4.3.2. Diclofenac (DIC)

DIC is an analgesic NSAID that exhibits antipyretic activity and is commonly employed to treat a range of acute and chronic diseases in both humans and veterinary populations. Nasiri et al. employed an innovative approach to detecting DIC through the use of AuNPs and a nanocomposite film consisting of functionalized multiwalled CNTs (f-MWCNTs) and GO.[112] Considering the electron transfer promotion between the target molecules and the electrode, the researchers decorated carbon-based nanomaterials by MNPs in the sensor selection. Firstly, the MWCNTs were chemically functionalized to reduce their hydrophobicity, and then were homogenized with GO in organic solution to prepare the f-MWCNTs-GO nanocomposites. The AuNPs were lastly electrodeposited on the surface of f-MWCNTs-GO modified electrode. The sensor prepared via this process was able to detect DIC oxidation in aqueous solutions while overcoming the aggregation issues associated with AuNPs alone and improving the overall electrocatalytic activity of the employed electrodes, which helps in increasing the efficiency of the sensor for rapid detection of the analyte. In a separate report, Eteya et al. utilized an electrode consisting of AuE modified with gold-platinum bimetallic nanoparticles (Au-PtNPs) and f-MWCNTs to successfully quantify DIC in both urine and pharmaceutical samples.[113] Similarly, a single-step electrochemical reduction strategy has also been employed to simultaneously synthesize a nanocomposite consisting of rGO and platinum nanoflowers (PtNFs) on an SPCE surface for DIC detection.[114] The presence of rGO on the composites could prevent the aggregation of PtNFs during the synthesis process. The resultant nanocomposite-based sensor exhibited a 5-fold rise in anodic peak current as compared to the unmodified electrode, enabling reliable DIC detection in prepared samples with 84–105% recovery rates.

4.3.3. Acetylsalicylic acid (ASA)

ASA, commonly known as aspirin, has remained one of the most commonly used NSAIDs since its initial discovery over 250 years ago owing to its potent analgesic, antipyretic, and anti-inflammatory properties. However, the widespread utilization of ASA has contributed to overdose-related issues, particularly among those who regularly consume this drug such as individuals with chronic inflammatory diseases. The need to reliably detect ASA and metabolites thereof in patient samples has spurred the development of many published electrochemical sensors. For instance, one group employed a one-stage electropolymerization strategy to synthesize a molecularly imprinted polymer (MIP) consisting of Ppy, sol-gel, and Silica@Gold core-shell NPs (SiO_2@AuNPs) on an AuE surface,[115] yielding a hybrid nanocomposite conducive to efficient electron transfer owing to its high surface area, excellent conductivity, and porous structure yielding abundant sites for selective recognition. In a separate report, Diouf's group utilized self-assembling chitosan capped AuNPs (Cs + AuNPs) on a SPCE to develop an electrochemical sensor capable of detective ASA in pharmaceutical tablets as well as in saliva and urine samples.[116] The AuNPs included in this platform reportedly overcome the electrically insulating activity of Cs, thus improving its conductivity and consequent catalytic activity. Recently, Li et al. utilized MWCNTs, thiolated polyaniline (tPANI), and gold-platinum core-shell nanoparticles (Au@Pt) to prepare a nanocomposite used to modify a GCE[117], thereby enabling the simultaneous detection of six over-the-counter drugs, including ASA, via voltammetric analysis. In this platform, more adsorption sites on the surface electrode were generated by combining harder NPs and softer organic materials, in addition to generating microstructural characteristics conducive to electron transport. The fabricated sensor exhibited good stability, sensitivity across a wide dynamic range, and reproducibility, making it well-suited to use in quality control and forensic applications.

4.3.4. Tramadol (TRA)

As an atypical opioid that agonizes the μ-opioid receptor, TRA is considered to be a generally safe analgesic when used as directed. However, prolonged abuse or inappropriate use of TRA can result in adverse side effects and a risk of dependence. Kolahi-Ahari prepared an electrochemical sensor capable of detecting this opioid by using an f-MWCNTs/AuNPs nanocomposite on a pencil graphite electrode (PGE),[118] enabling wide linear detection owing to the high specific surface area of the utilized f-MWCNTs and the consequent improvement in particle deposition together with the robust electrocatalytic activity exhibited by AuNPs, facilitating enhanced electron transfer between TRA and the surface of the electrode. A similar approach was also employed to generate an electrochemical sensor capable of simultaneously detecting TRA and epinephrine (EP) using a nanocomposite consisting of Pt-doped NiO/MWCNTs nanocomposite.[119] The resultant sensor was able to accelerate electron transfer reactions for TRA and EP while boosting corresponding oxidation signals, enabling both to be detected in real-world samples via DPV. In a separate study, researchers leveraged AgNPs to coat a poly-aniline layer (PANI-AgNPs) on the surface of a screen-printed AuE (Au-SPE),[120] as shown in Figure 8A. As a typical conductive polymer, PANI are extensively used to protect the MNPs from restacking for electrochemical sensor modification. Moreover, the combination of PANI with AgNPs resulted in creating synergistic effects such as a larger active surface area and a lower overvoltage. When DPV and EIS were used to monitor MIP electrochemical responses to TRA for this platform in 0.01 M PBS (pH = 7.2) containing $[Fe(CN)_6]^{3-/4-}$, increases in TRA concentrations were found to correspond to gradual decreases in $[Fe(CN)_6]^{3-/4-}$ anodic current peaks for DPV with corresponding R_{ct} increases for EIS (Figure 8B), thereby enabling TRA to be quantitatively detected across a wide range.

4.3.5. Piroxicam (PIR)

PIR is a NSAID that is commonly employed to treat a diverse array of diseases. Karimi-Maleh et al. developed a ZnO-Pd/CNT nanocomposite-modified GCE capable of readily detecting PIR and the anti-Parkinsonian drug levodopa (L-dopa) at the same time.[121] Owing to the excellent conductivity of ZnO-Pd/CNT, maximum oxidation currents for both of these drugs were detectable on the modified electrode surface, allowing for L-dopa and PIR to be, respectively, detected. Kong' group separately employed a nanocomposite consisting of PtNPs on nitrogen-doped rGO single-wall CNTs (Pt-N-rGO-SWCNTs) for the electrochemical detection of PIR via a DPV approach.[122] In electrochemical characterization studies, the authors found their nanocomposite to exhibit enhanced PIR detection activity attributable to the advantageous properties of the included compounds. In another exciting work, Dehdashti and Babaei have also reported the design of a Pt-doped nickel oxide NP (Pt-NiO) and MWCNT-modified GCE-based electrochemical sensor capable of analyzing PIR and amlodipine (AMD) levels in samples of interest.[123] In this system, Pt doping was found to result in significant increases in the available active surface area, boosting NiO electrochemical properties relative to those observed for pure NiO such that PIR and AMD could be, respectively, detected.

4.4. Antineoplastic drugs

Antineoplastic drugs are agents with cytostatic or cytotoxic activity that are used in the context of the chemotherapeutic treatment of cancer patients. These drugs are highly potent and can cause toxicity at even low concentrations in humans or environmental contexts,[145] making it essential that reliable approaches to monitoring for these agents be developed. Owing to their low cost and practical characteristics, electrochemical (bio)sensors have been of particular interest in this context. As such, in this section, we discuss recent advances in the design of metal nanocomposite-based electrochemical sensor platforms used to detect antineoplastic drugs (Table 4).

4.4.1. Flutamide (FLU)

FLU is a potent non-steroidal anti-androgen drug prescribed to inhibit testosterone-mediated prostate cancer cell growth. FLU is consumed in the form of a highly active prodrug capable of generating free radicals and potentially inducing DNA damage. It is thus critical that reliable approaches to detecting FLU in biological, pharmaceutical, and environmental samples be developed. To that end, one research team reported the development of an electrochemical FLU sensor through the electropolymerization of poly (bromophenol blue) (PBPB) as a redox mediator on a chitosan-Au collapse gel (CS-Au CG)-

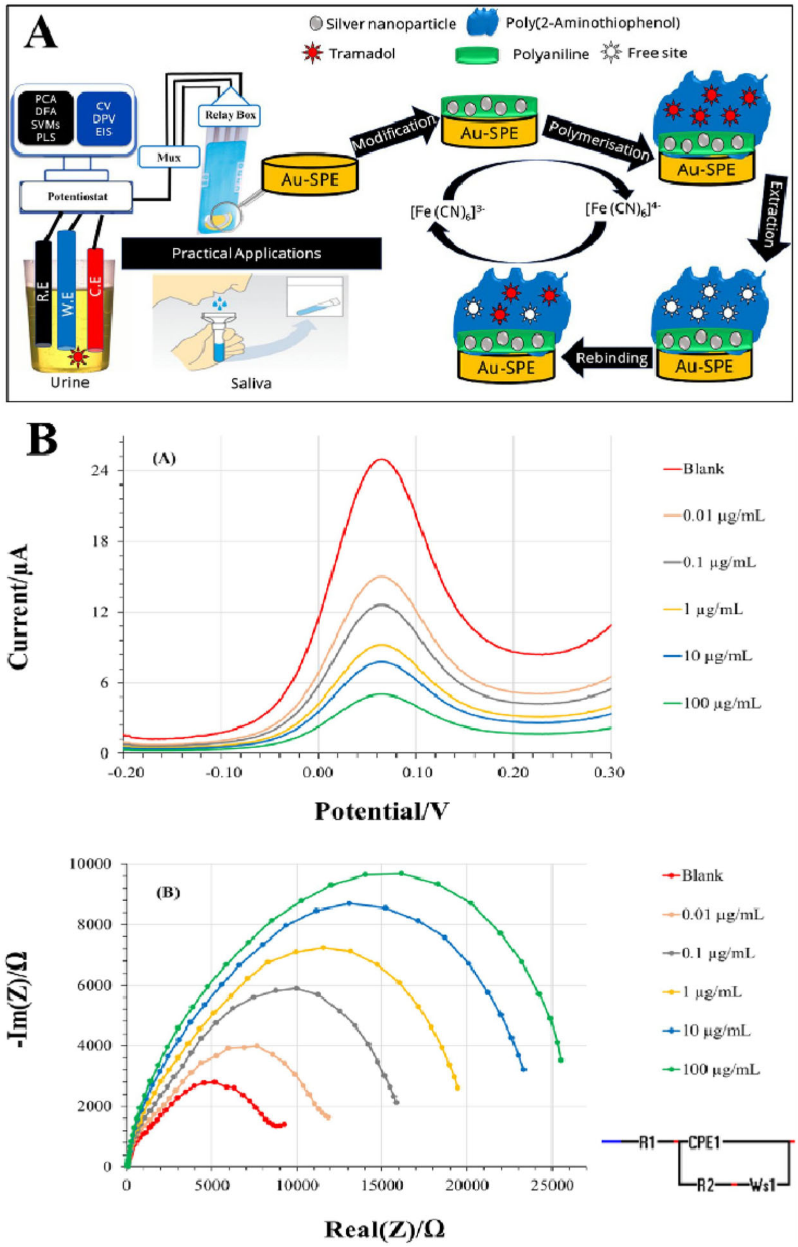

Figure 8. (A) MIP sensor preparation; (B) MIP sensor electrochemical responses to increasing TRA concentrations as measured via EIS and DPV (Reproduced from Ref.,[120] with permission from Elsevier).

modified GCE[146]. The resultant CS-Au CG/PBPB film exhibited markedly increased FLU electrocatalytic activity attributed to halogen-nitro synthon molecular recognition processes, enabling the detection of this antineoplastic drug via DPV with a low LOD and excellent sensitivity. In another case, researchers conducted the *in situ* modification of a GCE using a composite consisting of AuNP-decorated rGO and polypyrrole nanotubes (AuNP@rGO/PPyNT) through a nanosecond laser-based heating strategy.[147] The resultant sensor was able to simultaneously detect FLU and furazolidone, exhibiting excellent selectivity in the presence of interfering metal ions or chemical compounds, underscoring its potential real-world applicability. As illustrated in Figure 9A, Hwa et al. also designed a hexagonal Sn-doped ZnO nanocomposite anchored on rGO that, when used to modify the surface of a GCE, was able to detect FLU reduction in aqueous and biological samples.[148] In the sensor selection, the researchers considered the positive effects of combining ZnO with MNPs and carbon sourced nanosheets to increase ZnO conductivity. Compared to bare and other modified electrodes, a higher peak reduction current for Sn-ZnO/rGO/GCE was displayed, demonstrating that the proposed nanocomposite is a promising sensor material with good catalytic performance. This sensor was able to reliably detect FLU via DPV in a linear 0.01–170 μM range in 0.1 M of PBS (pH 7.0) with a 7.3 nM LOD (Figure 9B).

4.4.2. 5-Fluorouracil (5-FU)

At present, the antitumor drug 5-FU remains the gold-standard chemotherapeutic treatment for stomach, breast, cervical, pancreatic, and colorectal cancers. Zahed et al. reported the

Table 4. Selected applications for the analysis of antineoplastic drugs by using metal nanocomposite-based electrochemical (bio)sensors (2017–2022).

S. No.	Pharmaceutical compound	Modified metal nanocomposite	Electrode	Electroanalytical method	Linear range	LOD	Real sample	Ref.
1	FLU	CS-Au CG/PBPB	GCE	DPV	0.01–1245 μM	4.8 nM	Serum, urine	[146]
2		AuNP@rGO/PPyNT	GCE	DPV	0.01–1214.11 μM	2.45 nM	Serum	[147]
3		Sn-ZnO/rGO	GCE	DPV	0.01–170 μM	7.3 nM	Bovine serum albumin, serum, urine, river water	[148]
4	5-FU	AgNPs@PANINTs	GCE	DPV	1.0–300 μM	0.06 μM	Serum	[149]
5		Au@CS-PMAA semi-IPN nanogels	GCE	DPV	0.1–497 μM	0.03 μM	Serum	[150]
6		Pd–Au/MWCNT-rGO	GCE	DPV	0.05–75 μM	9.4 nM	Serum, urine	[151]
7	DOX	AgNPs/CS	GCE	SWV	103 nM–8.6 μM	103 nM	Cell lysate, human plasma	[45]
8		MWCNTs-COOH/AuNPs	GCP	LSV	0.01 nM–1 μM	6.5 pM	–	[152]
9		rGO/Au/PPy	GCE	CV	0.02 μM–25 mM	0.02 μM	Ampoule	[153]
10		AuNRDs/1T-MoS_2	SPE	DPV	0.01–9.50 μM	2.5 nM	Serum	[154]
11		Pd@Pt/MWCNT	GCE	AdSSWV	4.4–8580 nM	0.86 nM	Serum, urine	[155]
12		PAMT@AuNP@rGO	GCE	DPV	30 pM–30 μM	9.0 pM	Serum	[156]
13		CuNPs-CB-Nafion	GCE	SWV	0.45–5.1 μM	24 nM	River water, urine	[157]
14		AgNPs-CDs-rGO	GCE	DPV	0.01–2.5 μM	2 nM	Serum	[158]
15	Nilutamide (NLM)	(MWCNTsf –NGr/CTS)-Cu	GCE	DPV	0.005–20 μM 20–900 μM	1.6 nM	Tablet, serum	[159]
16		β-CD-AuNP/GO	SPCE	DPV	0.01–193 μM	0.4 nM	Tablet, serum	[160]
17	Topotecan (TPC)	AuNRDs/MI-GR	SPE	AdsDPV	0.1–16.0 μM	0.022 μM	Serum	[161]
		nano-AB-AuNPs	GCPE	SWV	1.99–671 nM	0.0164 nM	Serum, urine	[162]
18	Daunorubicin (DNR)	N-rGO-SWCNTs-Pt	GCE	DPV	19.5–10.638 nM	5 nM	Serum	[35]
19	Epirubicin (EP)	Ag-MWCNT	GCE	SWV	0.003–0.25 μM	1.0 nM	Serum, urine	[163]
20	Oxaliplatin (OXAL)	MIP-Ag@Cu-BDC / N-CNTs	GCE	DPV	0.056–200 ng/mL	0.016 ng/mL	Serum, urine, Oxitan®	[55]
21	Pemetrexed (PTX)	Pd/CNF/$[M3OA]^+[NTF2]^-$/Nafion	CPE	SWV	1–35 nM	0.33 nM	Pemetrexed powder, Cancerous plasma, urine	[164]

AuNRDs: gold nanorods; 1T-MoS_2: metallic phase molybdenum disulfide; AB: acetylene black; $[M3OA]^+[NTF2]^-$: methyl (trioctyl)ammonium bis(trifluoromethylsulfonyl)imid.

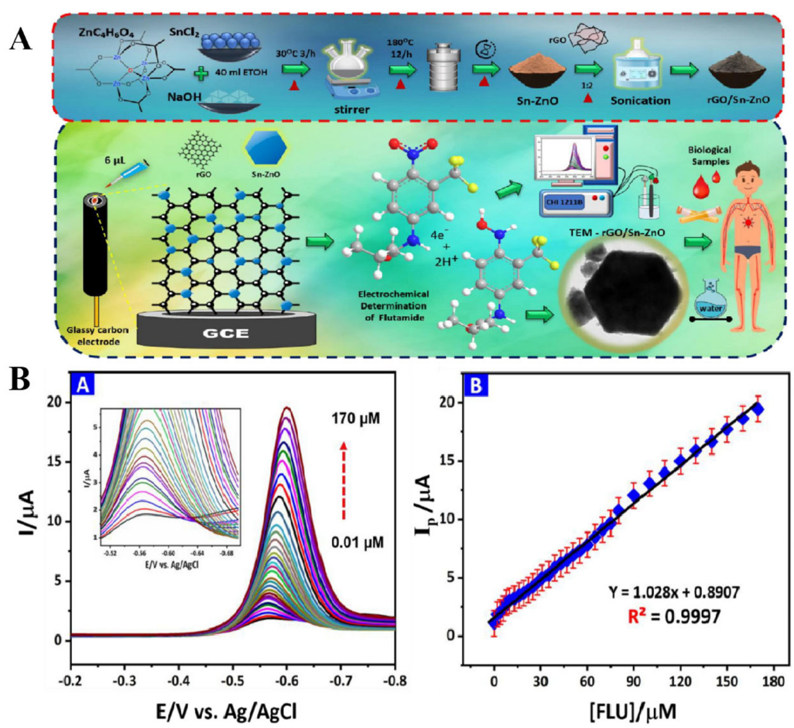

Figure 9. (A) Schematic overview of the modification and preparation of a Sn-ZnO/rGO nanocomposite for FLU detection; (B) Quantitative DPV-based FLU detection (Reproduced from Ref.,[148] with permission from Elsevier).

fabrication of an AgNP-polyaniline nanotube (AgNPs@PANINTs) nanocomposite used to detect 5-FU by doping AgNPs with PANI followed by their physical absorption onto the PGE surface.[149] DPV responses revealed maximal 5-FU peak current at a pH of 8.0, with a linear detection range, a low LOD, and high resistance to interference. In a separate report, researchers employed a drop-casting approach to synthesize a nanoreactor consisting of AuNPs embedded in a chitosan-poly (methacrylic acid) (Au@CS-PMAA) semi-IPN nanogel,[150] resulting in a sensor with electrocatalytic activity responses specific for 5-FU (Figure 10A). The colloidal stability of the prepared nanogel was demonstrated to be superior to that for CS-PMAA alone (Figure 10B), with a propped mechanism of action based upon 5-FU electro-oxidation attributable to strong H-binding interactions between this drug and the CS and PMAA -OH and -COOH groups

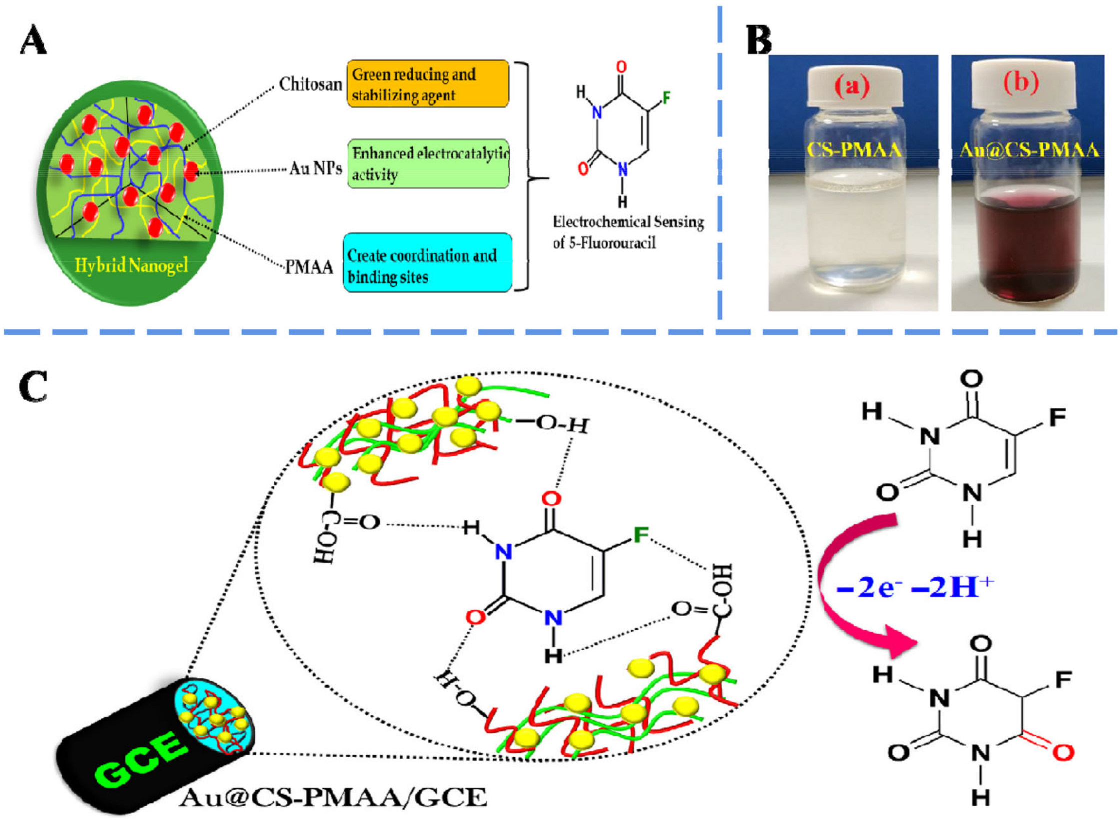

Figure 10. (A) Schematic overview of the design and potential applications of an Au@CS-PMAA semi-IPN nanogel for use in 5-FU detection; (B) Images of (a) CS-PMMA and (b) Au@CS-PMAA semi-IPN nanogel preparations; (C) The proposed mechanism of 5-FU electro-oxidation at the Au@CS-PMAA/GCE surface(Reproduced from Ref.,[150] with permission from Elsevier).

Table 5. Selected applications for the analysis of antipsychotic drugs by using metal nanocomposite-based electrochemical (bio)sensors (2017–2022).

S. No.	Pharmaceutical compound	Modified metal nanocomposite	Electrode	Electroanalytical method	Linear range	LOD	Real sample	Ref.
1	CLZ	Fe_3O_4/Ala/Pd	GCE	DPV	3–70 nM	1.53 nM	Tablet, serum	[166]
2		$RuTiO_2$/MWCNTs	CPE	SWV	0.01–0.07 μM	0.057 nM	Urine	[167]
3		Bi–Sn NP/CAG	SPCE	DPV	0.5–2092 μM	97.6 nM	Rat brain region serum	[168]
4		Rego-Pt	PGE	CV	0.05–10 μM	2.3 nM	Serum	[172]
5		Ru-TiO_2	CPE	SWV	0.9–40 μM	0.43 nM	Tablet, urine	[173]
6	CLZP	Fe_3O_4/R-SH/Pd	GCE	DPV	0.01–1 μM	3.02 nM	Tablet, serum	[169]
7		CS-Ag/N-GQD	AuE	DPV, SWV	84–625 μM 54–1000 μM	84 μM 54 μM	Human plasma	[170]
8		SFs – IL	GCE	DPV	0.1–250 μM	66 nM	Serum, urine	[171]
9	Chlorpromazine (CPZ)	Au/N-GOQDs/NiS_2/BC/MIP	GCE	DPV	0.005–2 μM	0.25 nM	Serum, urine	[174]

Rego: reduced graphene oxide; N-GOQDs: nitrogen-doped graphene oxide quantum dots

(Figure 10C). Currently, another group has proposed the design of a platform capable of simultaneously detecting 5-FU and Irinotecan (IRI) using a Pd-Au/MWCNT-rGO nanocomposite and a dual-signal electrochemical ratiometric approach.[151] When ferrocene (Fc) was included as an electroactive compound for reference, DPV peak currents for IRI (+0.58 V) and 5-FU (+1.17 V) exhibited gradual increases with rising concentrations of these drugs, whereas Fc peak current (+0.20 V) remained largely unchanged, thus enabling the selective and reproducible detection of both of these drugs through analyses of the (I_{IRI}/I_{Fc}) and ($I_{5\text{-}FU}/I_{Fc}$) signals.

4.5. Antipsychotic drugs

Antipsychotic drugs are commonly prescribed to treat a range of mental health disorders including anxiety, depression, and schizophrenia. Many of these drugs exhibit a high potential for toxic side effects and a relatively narrow effective therapeutic range,[165] underscoring the importance of being able to precisely measure their concentrations in a range of pharmaceutical contexts. Below, we therefore provide an overview of multiple electrochemical sensors that have been developed as tools for antipsychotic drug detection (Table 5).

4.5.1. Clozapine (CLZ)

As an atypical antipsychotic, CLZ has achieved great efficacy in the treatment of schizophrenia in individuals unable to tolerate other antipsychotic medications. Several strategies to detect CLZ in biological samples have been reported to date. In one study, Tammari et al. generated a Fe_3O_4, β-Alanine

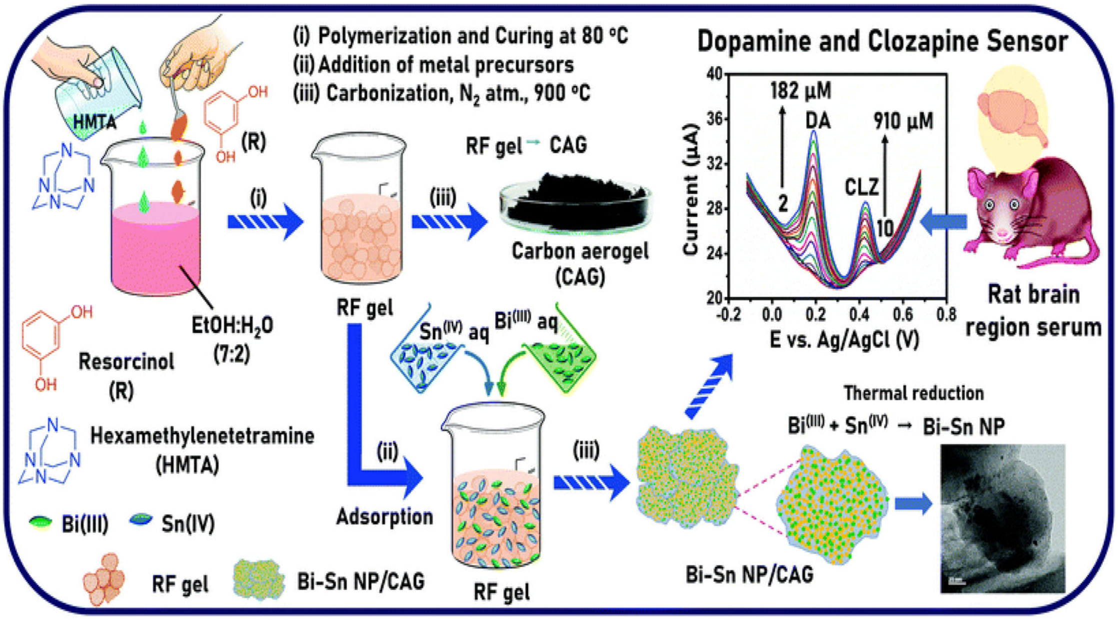

Figure 11. Schematic overview of the synthesis and characterization of a Bi-Sn NP/CAG nanocomposite, and the assessment of its electrochemical sensor performance (Reproduced from Ref.,[168] with permission from The Royal Society of Chemistry).

(Ala) and Pd (Fe_3O_4/Ala/Pd) magnetic nanocomposite with robust electrocatalytic properties and a high surface area, making the resultant modified electrode well-suited to the detection of CLZ-associated oxidation peak current in DPV analyses.[166] In another work, researchers designed a nanocomposite consisting of MWCNTs and Ru-doped TiO_2 ($RuTiO_2$) NPs in a carbon paste electrode (CPE) matrix that was then used to design a rapid voltammetric sensor used for CLZ detection via SWV[167]. In this system, CLZ exhibited diffusion-controlled behavior, with a notably amplified response at the electrode surface such that CLZ could be detected in human urine samples and clinical dosing preparations. Furthermore, Veerakumar et al. have also reported the design and fabrication of a nanocomposite consisting of ultrafine Bi-Sn NPs decorated on carbon aerogels (Bi-Sn NP/CAG) for use in the simultaneous electrochemical detection of CLZ and DA (Figure 11), with the resultant sensor platform being successfully used to detect these two analytes in samples of rat brain region serum.[168] In this case, the authors demonstrated that CAGs, with specific 3 D porous structures, can accelerate reactant diffusion and contact to the catalytic sites by offering sufficient space. The role of bimetallic nanoparticles were to provide rapid electron transfer, resulting in extraordinary electroanalytical efficiency. The presence of Bi-Sn NPs were also helpful for CAGs to preserve structural integrity.

4.5.2. Clonazepam (CLZP)

The benzodiazepine-derived CLZP is commonly prescribed as an anticonvulsant drug for the treatment of epilepsy patients, functioning best in the 15–80 ng/ml therapeutic concentration range at predose sampling. CLZP doses in excess of 120 ng/ml can be deleterious and may cause individuals to enter a comatose state, underscoring the importance of carefully monitoring the levels of this drug in biological samples. Lotfi et al. reported the synthesis of a Fe_3O_4, 3-aminopropyltriethoxysilane (APTES), cyanuric chloride (CC), 2-mercaptoethanol, and Pd nanocomposite that was cast on the surface of a GCE and used to detect CLZP[169]. The resultant sensor benefited from the increased surface area and electrocatalytic activity of the prepared nanocomposite, in which the presence of organic molecules on Fe_3O_4 improved covalent Pd adsorption, enabling the voltammetric detection of this drug in real-world samples as confirmed via HPLC analyses. Ashrafi et al. have also reported the development of an AgNP nitrogen-doped graphene QD-based conductive nano-ink (Ag/N-GQD) capable of efficiently quantifying the levels of CLZP and four other benzodiazepine drugs.[170] This sensor was prepared through the electrodeposition of this Ag/N-GQD nano-ink on a poly chitosan-modified AuE, with AgNPs improving the overall conductivity of this N-GQD-based hybrid system through the provision of significant electronic interactions to enhance overall charge transfer activity. This sensor was able to reliably detect the target pharmaceutical analytes via SWV and DPV without the need for sample pretreatment for standards and plasma samples. Khoshroo et al. also explore the use of a GCE modified with a nanocomposite consisting of Ag fibers and IL (SFs-IL) through electrochemically amplified detection,[171] yielding a wide linear detection range and a low LOD, exhibiting satisfactory CLZP detection in urine, serum, and pharmaceutical formulation samples.

4.6. Antihypertensive drugs

Antihypertensive drugs are prescribed in an effort to reduce blood pressure levels in hypertensive patients. Some patients require sustained oral consumption of specific antihypertensive agents in order to appropriately control their blood pressure, thereby reducing their risk of cardiovascular

Table 6. Selected applications for the analysis of antihypertensive drugs by using metal nanocomposite-based electrochemical (bio)sensors (2017–2022).

S. No.	Pharmaceutical compound	Modified metal nanocomposite	Electrode	Electroanalytical method	Linear range	LOD	Real sample	Ref.
1	AMD	GNRs-GO-fCNTs	GCE	DPV	0.01–75 μM	3 nM	Serum, plasma	[176]
2		Ag-$Ce_2(WO_4)_3$@CNF	GCE	DPV	0.01–130 μM	0.712 nM	Tablet, urine	[177]
3		CNTs–Au_{nano}	GCE	DPV	0.01–35 mM	0.65 nM	Human serum	[178]
4		COOH-CNTs/Ag/NH_2-CNTs	GCE	SWASV	50 pM–6 nM	77.6 fM	Serum, urine, tap & drinking water, artificial saliva, synthetic sweat	[181]
5		AgNPs/fMWCNT/Cu NP	CPE	ASWV	0.02–6.3 μM	0.516 nM	Amlodac, Amlopin, serum, plasma, urine	[182]
6		Pd-Ag/rGO	GCE	DPV	0.01–0.14 μM	0.007 μM	Urine	[183]
7		CeO_2–AuNFs/GO	GCE	DPV	0.01 μM–1 mM	0.002 μM	Pharmaceuticals, serum, plasma	[184]
8	PRO	CuNPs-GO-CB-PEDOT:PSS	GCE	SWV	0.5–2.9 μM	0.18 μM	Synthetic urine	[179]
9		AgNP-IL-FG-NF	GCE	SWV	0.1–2.9 μM	17 nM	Bovine serum, urine	[180]
10	Metoprolol (MTP)	GRE/PtNPs/NFN	GCE	AdsDPV	14.4 nM–7.5 μM	4.3 nM	Tablet	[185]
11	Captopril	Au@Cu-BTC	GCE	CV	0.5–7.0 μM 10–2500 μM	0.047 μM	Tablet	[186]

NFN: nafion; BTC: 1,3,5-benzenetricarboxylate.

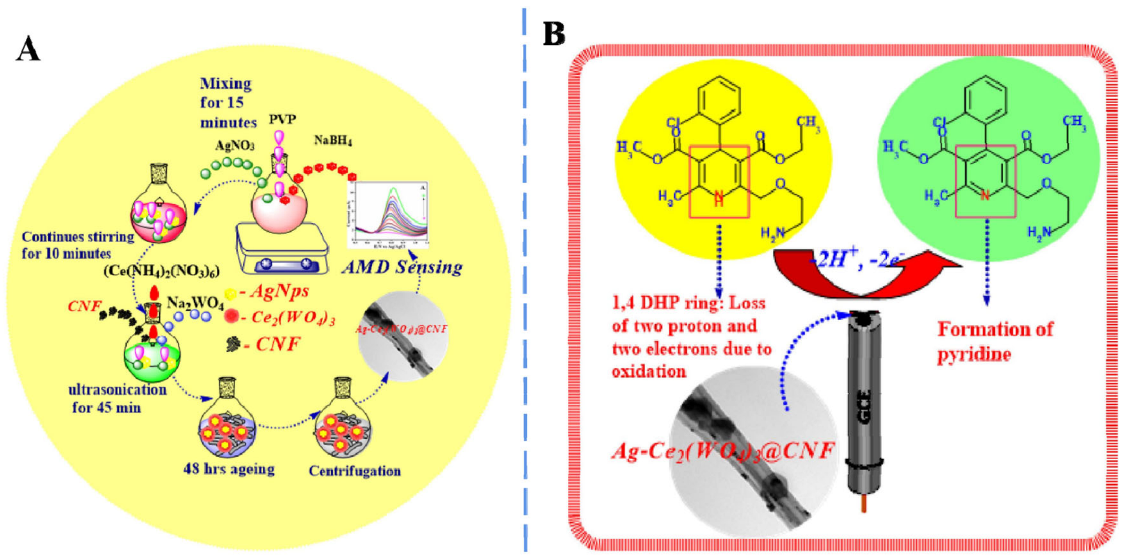

Figure 12. Schematic overviews of (A) Ag-$Ce_2(WO_4)_3$@CNF nanocomposite *in situ* synthesis; and (B) nanocomposite-based AMD electrocatalytic oxidation (Reproduced from Ref.,[177] with permission from Elsevier).

disease-related mortality.[175] However, there are some data from long-term clinical trials which suggest that these antihypertensive drugs can also contribute to cancer development. Below, we discuss recently published approaches to the electrochemical detection of a subset of these antihypertensive drugs (Table 6).

4.6.1. Amlodipine (AMD)

The third-generation antihypertensive dihydropyridine derivative AMD exhibits long-acting calcium antagonist activity, and is commonly prescribed for the treatment of hypertension and cardiovascular diseases. Arvand et al. fabricated a gold nanorod (GNR)-GO-functionalized CNTs (fCNTs) nanocomposite which, when used for electrode modification, reduced overpotential values and the electrode response time while increasing the overall electrochemical response and available surface area for electroactivity.[176] The resultant sensor was able to detect AMD in human blood samples. In another study, Sudha et al. reported the design of an AMD electrochemical sensor based on the use of a novel silver-cerium tungstate-decorated CNF (Ag-$Ce_2(WO_4)_3$@CNF) ternary nanocomposite synthesized through a combination of hydrothermal and ultrasonication approaches[177] (Figure 12A). The authors firstly modified AgNPs onto $Ce_2(WO_4)_3$ along with a sponge-like porous nanostructure, and then embedded them on the CNF to obtain Ag-$Ce_2(WO_4)_3$@CNF ternary nanocomposite. In the context of electrocatalytic reactions through the prepared nanocomposite, the electro-oxidation of the amine group in the pyridine position in AMD occurred, with $2H^+$ and $2e^-$ being involved in this oxidation process (Figure 12B). Under optimized conditions, this nanocomposite electrode was able to selectively, sensitively, and stably detect AMD. In a particularly recent study, researchers reported the formation of thiourea self-assembled monolayers (TU-SAMs) over gold nanoparticles mixed with carbon nanotubes (CNT-Au_{nano}) to prepare a nanocomposite film which, when used to modify a GCE, enabled simultaneous AMD, AP, dobutamine and daclatasvir detection via a DPV approach.[178] The proposed electrochemical sensor also exhibited good analysis performance in the human serum.

4.6.2. Propranolol (PRO)

The β-adrenergic blocking drug PRO is commonly prescribed to treat a range of cardiovascular conditions, including hypertension. PRO overdoses, however, can result in dangerous side effects including hypotension, bradycardia, bronchospasm, and even heart failure in some cases. Wong et al. modified a GCE with carbon black (CB), GO, CuNPs and poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate) (PEDOT:PSS) as electrode materials, enabling it to simultaneously detect caffeine, folic acid, isoproterenol, AP, and PRO owing to synergistic interactions among the included nanostructural components.[179] For the sensor preparation, carbonaceous nanomaterials, CB and GO sheets, were immobilized in the presence of PEDOT:PSS conducting reagent, forming a homogeneous film onto the GCE. After electrochemically deposition, CuNPs were evenly anchored on the CB-GO composite surface. Appropriate linear detection ranges and micromolar limits of detection were observed for all five of these analytes without any evidence of interference among measurements. Moreover, real sample detection was also tested with an acceptable recovery more than 90% in synthetic bio-fluids. Separately, researchers used AgNPs, IL, and functionalized graphene to modify a GCE such that PRO and salbutamol (SAL) could be simultaneously detected.[180] A range of scan rates and pH values were then used with this sensor platform to detect these two target drugs via SWV and CV, revealing data consistent with diffusion-controlled oxidation processes. Linear detection ranges for SAL and PRO were, respectively, observed from 0.079–2.9 μM to 0.10–2.9 μm, with respective detection limits of 13 nM and 17 nM. The proposed sensor was found to be effective as a means of simultaneously measuring the levels of these two pharmaceutical agents in urine and serum samples with satisfactory recovery levels.

5. Conclusion and future perspectives

In this review, several recent advances in the design of metal nanocomposite-based electrochemical (bio)sensors for pharmaceutical analysis have been summarized. These findings make it clear that significant progress has been made in efforts to design inexpensive, reliable, sensitive, and specific sensors capable of detecting a range of pharmaceutical agents by leveraging the unique functional properties of a variety of different metal nanocomposites. In particular, the combination of modern electrochemical systems with printing electrode technologies, such as screen printing, inkjet-printing, and 3 D printing, along with breakthroughs in micro-electronics and miniaturization permits the introduction of disposable and portable sensors for economic and practical feasibility. Such on-spot, in situ monitoring methodologies, when compared to conventional laboratory analysis, can reduce pretreatment steps, sample volumes and analysis time, allowing experimentalists to perform the measurements where they are needed the most.

Despite the advantages of these novel sensor platforms, however, several challenges still remain in this field, highlighting avenues for future research. For example, while metal nanocomposite size, morphology, dispersion, and specific surface area characteristics will all influence the properties of any fabricated sensor, many of these properties cannot be reliably controlled in the majority of synthetic contexts. There is thus a clear need to develop more advanced, precisely-controlled fabrication strategies tailored to the properties of the selected nanomaterials. In addition, while the majority of the sensors discussed herein were used to evaluate clinically relevant biofluid samples, they are not commercially available and have thus only been utilized at the laboratory scale owing to technical limitations including limited reproducibility and poor operational stability. These issues underscore the importance of combining electrochemical sensing and other approaches (such as LC, MS, field-effect transistors, or microfluidic chips) in real-world settings. Moreover, reliable miniaturized platforms compatible with the collection and transmission of data via smartphones and other wireless platforms will be conducive to the further simplification of analytical procedures and the improvement of overall portability. These challenges represent key research opportunities in this field in the coming years.

In conclusion, metal nanocomposite-based electrochemical (bio)sensors exhibit unique properties that make them promising tools for use in the detection of a diverse range of pharmaceutical agents, highlighting many avenues for future research and development. Further innovation in this rapidly-advancing field will ultimately aid in the design of advanced sensing platforms that can reliably detect drugs in a range of contexts, helping to protect human health and environmental integrity throughout the world.

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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