Nanomaterial-Based Electrochemical Sensors: Mechanism, Preparation, and Application in Biomedicine

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Nanomaterials possess unique properties, including excellent electrochemical properties, high surface area, and tunable electric conductivity, making them attractive for sensing applications, especially for electrochemical sensing. Notably, the compatibility of nanomaterials with other techniques opens up opportunities for electrochemical sensors in various biomedical applications. Herein, the enhancing mechanisms and preparation protocols of electrochemical sensors, regarding the material choices, are introduced. The integration of nanomaterial-based electrochemical sensors with other techniques toward precise health management and controlled drug release is further highlighted. It is concluded with perspectives on the future directions for this topic. Future research directions of nanomaterial-based electrochemical sensors and the challenges faced by commercialized implementation of the sensors are presented, paving the way for the upcoming era of accurate biosensing toward both academic and industrial use.

1. Introduction

In 1962, Clark et al. incorporated the enzyme glucose oxidase into a potentiometric measurement to determine glucose in plasma, opening up a new era of electrochemical biosensing.[31] Electrochemical biosensor measures the concentration of targeted analytes through the change of current, potential, conductance, or impedance, by oxidizing or reducing the analyte at an electrode.[2] Conventional electrochemical biosensing approaches focused on immobilizing various recognition molecules on electrodes, to serve as the bioreceptors or mediators of electron transfer and reduce or oxidize the target. However, the sensitivity and selectivity of electrochemical sensors are limited for biomedical use, concerning the low abundance of targeted analytes and strong interference in biosamples.[3] To overcome the limitations, nanomaterials are introduced into the development of novel electrochemical biosensing techniques.[4]

Nanomaterials with unique electrocatalytic properties,[5] strong adsorption capacity,[6] extremely small size,[7] large surface area,[8] and facile surface modification[9] have demonstrated their appropriateness for biosensing applications in the past decades.[10] In particular, nanomaterials play the multifunctional roles in electrochemical sensors, including 1) sample separation and preconcentration; 2) bioreceptor immobilization; and 3) signal enhancement.[2b,9a,11] The recent emergence of nanomaterials promised new prospects in designing the nanomaterial-based electrodes, enabling effective interactions and electron transfer between the analyte and electrode for electrochemical sensing. In this respect, the intelligent modification of nanomaterials onto electrodes leads to enhanced detection performance of biomolecules, even from complex clinical samples.[12] Another advantage of nanomaterial-based electrochemical sensors is that it can be further integrated into sensing-assisted devices (microfluidics, wearable devices, and drug carriers, etc.), thus shedding light on novel applications in biomedical science. The promising performance of electrochemical sensors was attributed to high electrocatalytic activity, simple devices, and high surface active sites. Electrocatalytic activity determines the efficacy of catalytic reaction, thus amplifying output signals and improving detection sensitivity.[13] The simple and cheap (≈$10 000) workstations facilitate the potential translation of electrochemical sensors into the clinical workflow. To compare with, thoughtful design should be taken into consideration, prior to applying other analytical technologies toward clinic applications (e.g., ≈$80 000 for Raman spectrometer, ≈$160 000 for mass spectrometer, and ≈$50 000 for fluorescence spectroscopy).[14] For detection speed, materials with high surface...
active sites can increase the current conversion efficiency of electrochemical sensors, shortening the detection time to second level.\[13\]

Despite of the current progress, the shortcomings of published results mainly involve the tedious electrode manufacturing and biological fouling phenomenon. For electrode manufacturing, the layer-by-layer assembling of functional materials and biomolecules on the surface electrodes is universally required, which is labor-intensive and demands for rational design.\[16\] For the biomedical applications, the electrochemical sensor is offset in real-case biosamples, due to the nonspecific binding between electrode surface and biofouling molecules from complex specimens.\[17\]

In the present review, we featured the latest progress and limitations in the field of nanomaterial-enhanced electrochemical sensors, as shown in Scheme 1. We first itemize different types of electrochemical sensors with special emphasis on nanomaterial choices for electrode modification. The added mechanism and preparation protocol are summarized in detail, to identify the challenges and future prospects associated with the design and development of certain nanomaterials. In addition, we highlight the recent advances of precise health management and controlled drug release in biomedicines. We foresee the further development of nanomaterial-based electrochemical sensors will bring in a continuous breakthrough to the coming era of personalized medicine.

2. Types of Nanomaterial-Based Electrochemical Sensors

In recent year, nanomaterials with controlled assembly have emerged as electrode materials, showing improved bioelectrocatalytic performance.\[18\] Here, we classify the novel electrochemical sensors into four types based on the nanomaterial chosen, including metal-, metal compound-, carbon-, and nanocomposite-based biosensors. In addition, we introduce the mechanism and preparation of the novel nanomaterial-enhanced sensors.

2.1. Metal-Based Nanosensors

Metals with designed nanostructure display enhanced electrochemical properties, due to the free movement of valence electrons.\[10b,19\] Within an electric field, the “free electrons” can pass through the lattice of metallic nanomaterials, enabling the current conduction in metals.\[20\] Therefore, metals (e.g., silver (Ag), gold (Au), platinum (Pt), and copper (Cu)) with excellent electrical conductivity are prepared onto the electrode surface, to enhance the detection sensitivity.\[10b,21\]

Song et al. dispersed Ag nanoparticles (NPs) onto bare gold electrode by wet chemistry approach, to amplify electrochemical signals of cysteine aspartase protease (Caspase-3, Figure 1A).\[22\] The assembly of Ag NPs not only prevented the conventional agglomeration but also enhanced the electrochemical signals by electron transfer between electrode and silver redox center. As a result, the detection of limit (LOD) for Caspase-3 was 24.62 pg mL\(^{-1}\), which was 65.75-fold lower compared to the classic absorption method.\[23\] Although silver NPs enjoy huge success in electrochemical biosensing applications due to unique electronic, optical, and catalytic properties, the intrinsic oxidizations along with low chemical stability restrict the long-term use of Ag-based nanomaterials as signal enhancement elements.\[24\] In contrast, gold is chemically stable. On the other side, the stable chemical property of gold should be taken into consideration because the redox reaction from Au\(^0\) to Au\(^+\) cannot occur spontaneously. Traditionally, corrosive acid solutions (e.g., HBr/Br\(_2\) mixture or HCl) are inevitable to facilitate the forward oxidation reaction, serving as both the oxidants by H\(^+\) and coordination agents by Br\(^-\)/Cl\(^-\).\[25\] In this context, Adaris et al. deposited Au NPs or Au NPs-Ab-BSA on screen-printed carbon electrodes (SPCEs) as the working electrode to perform the differential pulse voltametric measurements, considering the stability of gold (Figure 1B).\[26\] Corrosive acid solutions are universally required for the electrooxidation of the Au NPs\(^0\) tags to Au\(^+\) in the previously reported gold-based sensors, resulting in the environmental and safety concerns. To compare with, the
nontoxic NaNO$_3$ functioned as an oxidizing agent and NaCl as a gold chelating ligand in Figure 1B, to substitute the traditional corrosive acids and enable environmental sustainability by green chemistry. The authors for the first time used nonacid oxidants instead of the typical acid solution, to detect human matrix metallopeptidase-9 (hMMP-9) in spiked plasma with a tenfold improvement in LOD. However, the size and shape-dependent electrochemical properties of Au NPs are still unclear and wait for further studies. Alfredo and coworkers both experimentally and theoretically investigated the size effect of Au NPs (5, 20, and 80 nm of diameter) upon the electrochemical performance for the first time, using gold-modified electrodes as electrochemical transducers.[27] They modified the working electrode area of SPCEs by drip-coating approach based on the gold adsorption ability, and validated that the recognition event in an integrated biosensing system highly dependent on particle size due to Brownian effect.

In parallel to silver and gold, platinum and copper also demonstrate a strong current enhancement effect.[28] In 2021, Wu et al. developed a novel kind of 3D biosensor platform using Pt as conductive NPs, polyaniline (PANI) as polymer, and hollow fiber membrane (HFM) as a 3D scaffold (Figure 1C).[29] The gradient porous HFM scaffolds facilitated self-driven blood separation, based on uniform capillary force in a lumen and fluid diffusion in ordered pores. The optimized (3 mm) HFMs promised efficient blood separation for cells ranging from 6 to 20 μm, eliminating the potential bias induced by cell interference. Notably, this electrochemical sensor displayed high performance for glucose and cholesterol detection, such as little sampling consumption ($\approx$3 μL), fast fluid flow (>1 μL ms$^{-1}$), and wide linear range (0–24 mM for glucose with $R^2 = 0.992$; 0–9 mM for cholesterol with $R^2 = 0.999$). Razieh et al. prepared Cu electrodes by simple electrochemical deposition of Cu foam and bimetallic electrodes by galvanic replacement of Cu with Ag and Pt (Figure 1D).[30] The suggested electrodes displayed better nicotinamide adenine dinucleotide (NADH) regeneration yield than bare Cu foil, by enhancing electron/mass transfer rate through electrode porosity. But, a major drawback of metal-based electrochemical nanosensors is their expensive cost and untransparent look. In conclusion, new metal nanomaterials are necessary to achieve simple, fast, clean, and precise biosensing, among which bi/multimetallic alloys may enhance the efficacy of electrochemical sensors through heterogeneous structure and synergic effect.

2.2. Metallic Compound-Based Nanosensors

The conduction mechanism of metal compounds is generally lattice vibration, impurities, lattice defects (such as dislocations), grain boundaries, vacancies, surface or other deviations from ideal atoms, etc.[31] In particular, lattice vibration, impurities, and lattice defects are the main contributors to improve the electronic conduction of metal compounds. For lattice vibration, the electric conductivity of metal compound is influenced by the collision between phonons and free electrons in crystalline lattice.[32] For impurities, the insertion of carbon/nitrogen atoms
will cause an increase in the density of states near the Fermi level. Therefore, the lattice customization strategy provides enhanced conduction paths for carriers, effectively activating redox reactions and promoting electron transfer.\textsuperscript{[14a,13b]} For lattice defects, more vacancies are produced due to the missing atom from its original lattice site, which is beneficial to capture electrons and improve catalyst activity. In summary, tuning the lattice configuration is a promising method to improve detection performance of metal compound-based biosensors.\textsuperscript{[14b]} For example, metal oxides are generally ionic crystals, and the conduction mechanism is related to lattice defects.\textsuperscript{[20c,35]} Stannic oxide conducts electricity because of the existence of lattice oxygen vacancies, showing positive charge regions. There are some other metal compounds, especially composite metal compounds, which contain impurities or deviates from the stoichiometric ratio, showing excellent electrical conductivity.\textsuperscript{[36]}

Metal oxides with higher electron mobility,\textsuperscript{[37]} ionic conductivity,\textsuperscript{[38]} active sites,\textsuperscript{[39]} and layer-dependent bandgap\textsuperscript{[40]} are promised for nanomaterial-based electrochemical sensors. In 2018, Li et al. utilized the high adsorption of copper oxide (CuO) NPs toward biological samples to label targeted proteins. After HCl treatment, Cu\textsuperscript{2+} ions were deposited onto a glassy carbon working electrode (GCE). This CuO NP-based signal conversion and amplification achieved sensitive analysis of trypsin (LOD of 0.005 μg mL\textsuperscript{-1}, Figure 2A).\textsuperscript{[41]} In addition to the electric properties, metal oxides also possess unique optochemical features, shedding light on the molecular detection. Si et al. surface engineered the titanium dioxide (TiO\textsubscript{2}) anodic material by inorganic-framework molecular imprinting for electrochemical sensing of bisphenol A. The low LOD of 0.095 μM was attributed to the strong molecular recognition and superior anodic degradation (Figure 2B).\textsuperscript{[42]} Furthermore, the designed TiO\textsubscript{2} anodic material played dual functions, activating both as an electrochemical and a photochemical catalyst. The electro- and photo-assisted TiO\textsubscript{2} sensor was highly renewable, with an electrochemical signal decrease less than 5.0% in 10-run cyclic tests.

In addition to the metal oxides, certain metal sulfides also serve as the promising semiconductor materials for electrochemical application. For example, molybdenum disulfide (MoS\textsubscript{2}) has been emerging as one of the most efficient catalysts, due to the favorable redox electrochemical characteristics.\textsuperscript{[43]} Vishnu and coworkers modified pencil graphite electrode (PGE) with MoS\textsubscript{2} by single step growth via hydrothermal method, to detect DNA nucleobases (e.g., guanine and adenine, Figure 2C).\textsuperscript{[44]} Compared to bare PGE, MoS\textsubscript{2}-PGE displayed lower charge transfer and higher exchange current density, indicating the potentials as an electrochemical sensor for biosensing applications. However, the fabrication of MoS\textsubscript{2} by liquid-phase based scalable exfoliation is time consuming and labor-intensive, impeding their large-scale production and integration. Zhang et al. first synthesized electrochemically exfoliated MoS\textsubscript{2} flakes and deposited the as-prepared nanomaterials onto gold electrodes, acting as a novel sensing system for the detection of Ebola virus (Figure 2D).\textsuperscript{[45]} The constructed biomedical device consisted of 12 working sensors displaying Schottky junction characteristics with a satisfying analytic performance (LOD ~ fM). Overall, metallic compound-based Schottky biosensors facilitate the precise and cost-effective detection, holding promise in the precise detection of biomarkers toward biomedical applications.

2.3. Carbon-Based Nanosensors

Carbon-based materials, such as graphite, graphene, graphene oxide (GO), reduced GO, polymers, and carbon nanostructures, are often used as redox electrodes for clinical applications, due to their unique chemical properties and structural diversity.\textsuperscript{[46]}
Their diverse morphologies and chemical properties are correlated to the changes in sp, sp², and sp³ hybridization, resulting in superior electrical conductivity.[47] Specially, graphene structure is one of the most popular carbon materials for modifying electrodes, as it has a large usable potential range due to the extended π bond and sp³ hybridized carbon atoms.[48] Wu et al. drip-coated the functionalized graphene onto GCE in an array manner, serving as a sensor array featuring receptors of multiple tumor cells, including different cancerous, multidrug-resistant cancerous, and metastatic human breast cells (e.g., A549, HeLa, HepG2, K562, MCF-7, MDA-MB-231, MCF-7/ADR, NIH-3T3, PC-12, and HEK-293T), as well as artificial circulating tumor cell samples (CTC, Figure 3A).[49] Notably, the mechanism of cell adhesion to the sensor surface was the electrostatic and hydrophobic interaction between the sensor array and the cell surface.[50] The interaction of the cells with the functionalized graphene array depended on the surface properties of cells; therefore, each cell line possessed a unique electrochemical response to the functionalized graphene array. However, no specific binding (e.g., antigen–antibody recognition) were used in this work, which placed strained access to highly specific applications to certain targeted cells. Conjugating two graphene recognition elements together leads to an enhanced LOD down to single-cell resolution. It is worth noting that graphene is easy to aggregate during the electrode preparation process due to the strong π–π interaction, leading to loss of the active surface area and reduction of the electrochemical performance.[51] Hong et al. utilized direct-laser-writing to pattern 3D porous graphene framework (3DPGF)-based electrodes on indium-tin oxide (ITO) glass. (Figure 3B).[52] Importantly, the novel 3DPGFs–ITO electrode exhibited a large surface area and abundant edge-plane-like defective sites, beneficial for the development of sensitive electrochemical sensors.

In parallel to graphene derivatives, carbon nanostructures also demonstrate improved conductivity through π–π interactions. Our group is dedicated to developing ultrasensitive biosensors based on various carbon nanotubes (CNTs). In 2019, we directly modified CNT composites on the electrode to enhance electronic conductivity by 6.2-folds and reduced overpotential with a shift of 77 mV.[53] Hereafter, the group continued to report another label-free sensor to detect transferrin receptor with LOD of 0.082 ng mL⁻¹, by self-assembling the carboxylated multiwalled CNTs onto ITO electrodes.[54] On the contrary, Chen et al. oriented single wall CNTs (SWCNTs) onto the electrode surface to form vertically aligned nanostructures for electron transfer (Figure 3C).[55] The terminally activated SWCNTs can fix the heterogeneous electron transfer between the electrode and the detection environment, and the low-dimensional monolayer of sp² hybrid structure achieved noncovalent adsorption of single-stranded nucleic acid through π–π stacking. Therefore, the recognition efficiency of the SWCNT-based biosensor was greatly improved, showing a low LOD of 3.5 fM.

Except for the electrodes modified with CNTs, the novel electrodes made of CNTs have attracted intensive attention due to the facile fabrication and robust signal transducing. Jiang’s group reported a functionalized single nanowire electrode, for the electrochemical quantitation of NADH release from intracellular mitochondria (Figure 3D).[56] The authors first functionalized SiC@C nanowire, injected the material into glass micropipette, and protruded it to a length of 10 μm, to serve as a novel electrode for biosensing. In particular, CNTs promoted electron transfer, thus endowing the nanowire electrode with high sensitivity and selectivity.

Figure 3. Carbon-based electrochemical sensors. A) Seven functionalized graphene probes serving as the electrochemical sensor array to identify multitype cells. Cell adhered to the sensor surface based on electrostatic and hydrophobic interaction. Reproduced under the terms and conditions of the Creative Commons Attribution 4.0 International License.[49] Copyright 2017, The Authors, published by Springer Nature. B) The development of 3D porous graphene frameworks-based electrode with a large surface area. Reproduced with permission.[52] Copyright 2018, Royal Society of Chemistry. C) Schematic diagram of the electrochemical signal transduction principle of single wall carbon nanotube-based electrode for miRNA-21 sensing. Reproduced with permission.[55] Copyright 2019, Royal Society of Chemistry. D) In situ monitoring of NADH using a functionalized single nanowire electrode. Reproduced with permission.[56] Copyright 2020, Royal Society of Chemistry.
Overall, the proposed carbon-based nanosensors showed high-sensitive, fast, and accurate detection by improved conductivity. In particular, the fast detection was achieved by improved conductivity, due to the fast electronic transfer from physical aspect and readily redox reaction from chemical aspect. From physical aspect, the π–π bond of carbon nanomaterials allows the electric charge carrier to travel freely in the entire lattice, which improves the speed of electron transport. Correspondingly, the enhanced conductivity enables rapid transmission of electrochemical signals. In particular, the dynamic electron behavior of CNTs is close to the ideal Nernst equation, due to the fast movement of electrons (light speed). Compared with reverse transcription–polymerase chain reaction with whole process taking 1 h for coronavirus disease 2019 detection, the use of CNT electrodes demonstrated a faster electrochemical response and shorten the test time to 30 s. From chemical aspect, carbon nanomaterials are easy to be modified with functional groups (–OH and –COOH) as active sites, accelerating the electrochemical reaction. In a short time, more electrons are produced from the electrochemical reaction and converted into signal output, which can greatly shorten the measurement time.

As a limitation of the current works, the tedious layer-by-layer assembling of carbon-based nanomaterials onto electrodes is worthy further concern, when applying the sensors into the translational practice.

2.4. Nanocomposite-Based Nanosensors

The aforementioned nanomaterials have been widely used in electrochemical sensing, while still facing drawbacks when used alone. For instance, the easy aggregation of graphene layers severely weakens the detection performance, due to the strong π–π stacking and van der Waals forces between graphene sheets. In this regard, an urgent need has arisen to develop advanced electrode materials through reasonable composition optimization and interface modification.

The major solution is to stack distinct conductive nanomaterials to construct new types of heterostructure materials, thus combining the advantages of each building component while eliminating the corresponding disadvantages. Typically, regions depleted of free charge carriers are formed on either side of the pn junction in semiconductors, thus exhibiting low current efficiency. Chen and coworkers constructed sensors by drop-casting the Au-decorated (MoS₂–Au) nanoflakes onto the interdigitated electrode-incorporated poly(ethylene terephthalate) substrate and compared the performance of MoS₂–Au in detecting volatile organic compounds to pure MoS₂ nanoflakes (Figure 4A). A density functional theory calculation elucidated the stronger binding energy of acetone on MoS₂–Au (−0.573 eV) than that of bare MoS₂ (−0.293 eV) because of the increased electron-donating effect of Au NPs. Another MoS₂–Au-based nanoprobe with amplification effect were established in 2020. The ultrasensitive analysis of microRNAs was achieved by this platform, with LOD down to 0.038 fM. Similarly, Ma et al. also designed heterostructures of 2D MoS₂-on-nitrogen-doped carbon as electrode materials to improve the electrochemical performance. Another work has been reported employing CuO as a p-type semiconductor, nickel nanomaterials as a conducting metal, and PANI as electrically conductive polymers, to construct the electrode for glucose electrochemical detection (Figure 4B). Compared with other previously reported nonenzymatic glucose sensors, this electrode enjoyed a low LOD of 130 nM, showing a maximum tenfold decrease.

To address the instability of carbon-based electrode, complex composites are emerging as a better alternative and thus have

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**Figure 4.** Nanocomposite-based electrochemical sensors. A) The functioning mechanism of the hybrid MoS₂–Au-immobilized sensor. Reproduced with permission. Copyright 2019, American Chemical Society. B) Manufacturing process of the working electrode in a nonenzymatic glucose sensor, consisting of semiconductor, nickel, and polymer. Reproduced with permission. Copyright 2019, Elsevier. C) An aptamer sensor with working electrode functionalized with graphene-modified nanocomposites. Reproduced under the terms and conditions of the Creative Commons Attribution 4.0 International License.
been considered a hot topic in the field. Jian et al. integrated magnetic metal-organic framework NPs and TiO₂ nanotube arrays into an all-in-one portable system, for CTC capture and disease diagnosis based on cancer cell numbers.[71] In addition to the use as a catalyst (Fenton reaction) on semiconductor chip, the released iron ions also acted as the signal probe in the electrochemical measurement for cell quantifications. Wang’s group developed a biosensor by combining the screen printing of a graphene-modified nanocomposite electrode onto an origami paper-folding for sample processing and detection (Figure 4C).[72] The detection signal was greatly improved by accelerating the electron transfer rate through Au–S bonds.

In summary, the mechanism of electrochemical signal enhancement includes inhibiting charge recombination, promoting interface charge transfer, improving current conduction efficiency, and providing additional reactive sites. For charge recombination, electrons are avoided from being injected back into electrolyte from electrode surface in an ideal circumstance.[64] Carbon-based materials have large surface area to inhibit the charge recombination, thus can enhance the detection sensitivity and shorten the response time of the biosensor.[73] For charge transfer, the movements of electrons from sensors to redox probes are enhanced, by reducing the diffusion behavior of the probe in electrolytes.[74] Metals and carbon nanomaterials can be effectively used as electron conduction media, thus can promote charge transfer behavior at the sensor interface.[73a,75] For current conduction, the band structure of the nanomaterial affected the amount and migration rate of free electrons according to Faraday efficiency.[76] Doping oxides with transition metals can change the band structure and valence of active sites, leading to charge redistribution and enhancing electrochemical performance.[77] For reactive sites, a larger electrode surface area accommodates more reactive sites and enhances the surface loading of ligands. The high active surface/volume ratio of carbon- and metal-based materials can improve the interaction between the analyte and biosensing surface, and realize the effective transduction of biometric signals.[78] Therefore, the advanced electrochemical sensors can be customized with corresponding capabilities, by conjugating multiple materials based on the aforementioned mechanisms. Composite materials can effectively inhibit charge recombination, promote interface charge transfer, improve current conduction efficiency, and provide additional reactive sites, thus will potentially become the mainstream biological sensing tools in the future.

3. Biomedical Applications

Based on the precise recognition of biomolecules,[68,79] subcellular organisms,[80] and cells,[71,81] the nanomaterial-based biochemical sensors can be integrated with other devices (e.g., microfluidics and wearable devices) toward health management and therapeutic controlling systems.[82]

3.1. Health Management

Molecular biomarkers can be used for cancer diagnosis, staging, prognosis, risk assessment, and treatment selection.[106,83] Notably, small molecules serve as direct signatures of biochemical activity and are associated with disease genesis.[84] Zhang et al. detected two small molecules using biosensors (Figure 5A), such as amyloid oligomer (AβO) and adenosine triphosphate (ATP).[85] They developed dual-aptamer-based multi-electrode arrays for the simultaneous detection of AβO and ATP in artificial cerebrospinal fluid. The obtained dual-target aptasensor exhibited linear detection for ATP ranging from 10 pM to 1000 nM with a LOD of 2 pM, and linear detection for AβO ranging from 1 pM to 200 nM with a low LOD of 0.3 pM. Similarly, Vaneev and coworkers utilized a noble metal-based electrochemical sensor with platinized nanoelectrodes to detect the reactive oxygen species (ROS) signal.[78a] They validated the feasibility of nanoelectrode for in vivo measuring ROS in tumor-bearing mice, to monitor the efficacy of anticancer drugs on ROS pathways in real time.

Exosomes are extracellular vesicles (40–140 nm of diameter) released by cells and are detectable in most biofluids.[86] However, the rare existence of cancer-derived exosomes places clinical interest in both effective extraction and sensitive identification.[87] Fu et al. reported an electrochemical assay using magnetic NPs to selectively capture two markers (α-synuclein and synthetic-1) from neuronal exosomes (Figure 5B).[88] The cohort study of α-synuclein level across 40 clinical samples was conducted to distinguish Parkinson’s disease patients (n = 20 per group) from healthy controls toward precise diagnostics. In the latest work, a Korean group implemented a detachable microfluidic device with an electrochemical aptasensor, facilitating the specific, sensitive, and rapid detection of cancerous exosomes from plasma samples of breast cancer patients.[80a] Increasing the size of microorganisms up to micrometer, many groups extended the limit of electrochemical sensing to cellular scale. Tang et al. proposed sensitive electrochemical techniques to detect breast cancer cells by multifunctional self-assembling peptide nanofibers.[89] In addition, Suhito et al. proposed a multifunctional platform that could both monitor cell viability without damaging the cells and simultaneously evaluate the anticancer effects of curcumin in a brain tumor model.[90]

The ultimate goal of electrochemical biosensor research is to be applied in wearable devices. Current studies mainly focus on improving sensing performance, as well as assay robustness in various physical conditions.[91] Drug monitoring benefits the personalization of treatment based on pharmacokinetic and therapeutic evaluation.[92] Tai et al. presented a wearable band with nanodendritic materials, to continuously monitor caffeine from human sweat (Figure 5C).[93] In 2018, they further extended the targeted drug to Levodopa, i.e., a treatment for Parkinson’s disease.[94] Specifically, gold nanodendrites with large surface areas were synthesized via an overpotential deposition approach on the evaporated Au/Cr conductive layer, offering adequate interfaces for enzyme loading and molecular sensing. The performance of prolonged, continuous, and noninvasive drug monitoring in human subjects enabled dosage optimization in a point-of-care and precise manner. Other than drugs, Chen et al. designed an attachable, lightweight, and bendable bandage-based wearable sensor to detect lactate from human perspiration.[95] Distinct from single biomarkers, one of the current challenges in designing an ideal wearable device is to achieve the detection of multiple biomarkers in parallel.[96] A study reported a microneedle-based electrochemical sensor for the ingenious and simultaneous detection of lactate and glucose in artificial
interstitial fluid (Figure 5D). The analytical capability was promising as a real-time wearable device for continuous monitoring of lactate and glucose for sports medicine and biomedical applications.

Health management relies on mining big health care data produced in real-time subject monitoring. The noninvasive and cost-effective wearable devices based on electrochemical biosensors have made substantial progress in

![Diagram](image)

Figure 5. Health management based on nanomaterial-enhanced electrochemical sensors. A) Electrochemical dual-aptamer biosensor for the simultaneous detection of amyloid oligomer and adenosine triphosphate. Reproduced with permission. Copyright 2020, Royal Society of Chemistry. B) Facile impedimetric analysis of electrochemical biosensor to detect exosomes. Reproduced under the terms and conditions of the Creative Commons Attribution License (CC-BY). Copyright 2020, American Chemical Society. C) The mechanism of wearable sweat sensor for noninvasive levodopa monitoring and drug sensing. Reproduced with permission. Copyright 2019, American Chemical Society. D) Electrochemical microneedle sensor for simultaneous lactate and glucose monitoring. Reproduced with permission. Copyright 2019, Wiley-VCH.

![Diagram](image)

Figure 6. Drug release based on nanomaterial-enhanced electrochemical sensors. A) Controlled drug loading and release by electrochemical signals. Reproduced with permission. Copyright 2019, Wiley-VCH. B) A graphene-mixed array with skin-fitting property for diabetic monitoring and treatment. Reproduced with permission. Copyright 2016, Springer Nature. C) A wireless smart contact lens used for noninvasive glucose monitoring and controlled drug delivery. Reproduced with permission. Copyright 2020, The Authors, some rights reserved; exclusive licensee American Association for the Advancement of Science.
providing accessibility and field analysis of human health conditions.

3.2. Drug Release

Targeted and localized drug delivery systems have received significant attention due to the high demand for efficient functionality and reducing side effects of therapy. Targeting and penetration ability of drug delivery are challenging issues in this field. The electrochemical sensor provides an opportunity for drug delivery systems with precise temporal and spatial control. Woeppel et al. precisely controlled the drug release from the sulfonated silica NP-doped composite by electrochemical method (Figure 6A). In this article, SiO$_2$ NP dopants not only provided a potential drug delivery library but also maintained favorable electrochemical properties. Controlled release of DOX within a few seconds were achieved by the electron injection into doxorubicin (DOX)@nanographene oxide/platinum micromachines, with the reduced nanographene oxide serving as a drug-loading platform. Lee et al. demonstrated an integrated theranostic platform for diabetic monitoring and treatment, consisting of graphene-mixed arrays of skin-fitting devices (Figure 6B). The device enabled glucose and pH monitoring with a sweat control layer and diabetic treatment with temperature-responsive microneedles. A cascade reaction occurred when sensing high glucose concentration over the threshold, with triggering the microneedle to release metformin as feedback to deliver the percutaneous drug to the glucose sensor.

Probable concerns arise during the development of health devices based on electrochemical sensors, with environmental burden, resource waste, and low human compliance, when developing too many duplicated devices. Li et al. avoided the unnecessary wastes, by integrating controlled drug delivery system into a smart contact lens (Figure 6C). The multifunctional intelligent contact lens was designed with platinum nanostructures, showing low electrical resistance, high sensitivity, and stability for real-time electrochemical glucose reaction. Considering the drug release induced by accurate sensing in drug delivery systems, we anticipate the novel combination of electrochemical sensors into health devices will worth further investigation in biomedicines.

4. Conclusion

Nanomaterials have found extensive applications in the electrochemical field, with selectivity, sensitivity, specificity, chemical stability, electrocatalytic activity, and reproducibility attributes. Here, we describe the classification types and bioapplications of nanomaterial-based electrochemical sensors in biomedical area. For the types, we classified the current electrochemical sensors according to the enhancement by tuning the material compositions, with a detailed summary of the enhancing mechanisms and preparation approaches. For the bioapplications, we highlight the applications of electrochemical sensors coupling with wearable devices, microfluidics, and drug nanocarriers for health management and controlled drug release.

From the perspective of the future development of nanomaterial-based electrochemical sensors, we anticipate three major challenges to be addressed following this review, including the following: 1) the development and preparation of designed nanomaterials with enhanced electrochemical properties; 2) the biosafety issues toward in vivo testing and therapeutic applications; and 3) the implementation of artificial intelligence into the big health care data produced by point-of-care sensors.

In summary, nanomaterial-based electrochemical sensors are accompanied by high electrocatalytic enhancement and electronic conductivity, therefore have important practical value in the fields such as disease diagnostics and personalized therapeutics. Further developments of nanomaterial-based electrochemical sensors will have far-reaching implications to the research of precision medicines.

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Conflict of Interest

The authors declare no conflict of interest.

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