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Bioactive metallic nanozymes-based electrochemical biosensors for biomarker detection: Progress and prospects

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ABSTRACT

Nanozymes, as a branch of artificial enzymes, break the constraints of natural enzymes for instance their expensive cost, difficult purification and poor stability. In recent years, with the rapid development in nanosynthesis technology, catalytic analysis, biosensing, and materials theoretical computation, the researches on nanozymes have made remarkable progress. The unique advantages of nanozymes make them promising to replace natural enzymes in many typical applications. Among them, metallic nanozymes have received much attention in electrochemical sensing due to their excellent catalytic activity, stability and electrical properties. To help researchers understand the current investigations of metallic nanozymes, the recent research progress of metallic nanozymes from materials to electrochemical sensing applications are presented. The enzyme-like catalytic activity of metallic nanozymes and single and multi-metal component metallic nanozymes are described. Factors affecting the activity of metallic nanozymes are briefly discussed. We also discuss the wide range of applications of metallic nanozymes in electrochemical biosensing. The directions and challenges of metallic nanozymes in electrochemical sensing are discussed and summarized. The authors expect that this review will inspire the research of metallic nanozymes in electrochemical sensing and facilitate the development of nanozymes.

1. Introduction

The advances in bioscience, information science and materials science have promoted the rapid advancement of biosensing technology. The excellent sensitivity, rapid response time, affordability and portability of electrochemical techniques make them one of the ideal analytical tools for determining the concentration of biologically active molecules [1]. The earliest known reported prototype on electrochemical biosensors is the determination of glucose concentration based on the Clark and Lyons enzyme electrode system [2]. Since then, electrochemical sensors constructed on the basis of electrochemical technology have received more and more attention are considered to be a type of biosensors with great prospects for application development. Because of their superior catalytic efficiency and substrate selectivity, electrochemical sensors constructed using natural enzymes as biocatalysts exhibit exceptional selectivity for target analytes in detection applications [3–5]. Whereas, due to the poor conductivity of natural enzymes, their application in electrochemical sensors is limited when relying only

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on their catalytic capabilities for sensing [6]. Due to the sensitivity of natural enzymes to environmental influences, enzyme-based electrochemical sensors usually need to be used and stored in specific environments. Furthermore, the intricate immobilization procedure of enzyme has the potential to diminish or completely deactivate the native enzyme activity. Difficulty in purification of natural enzymes as well as low reusability also contribute to the high cost of their application [7].

The quest for materials that can replace natural enzymes has drawn

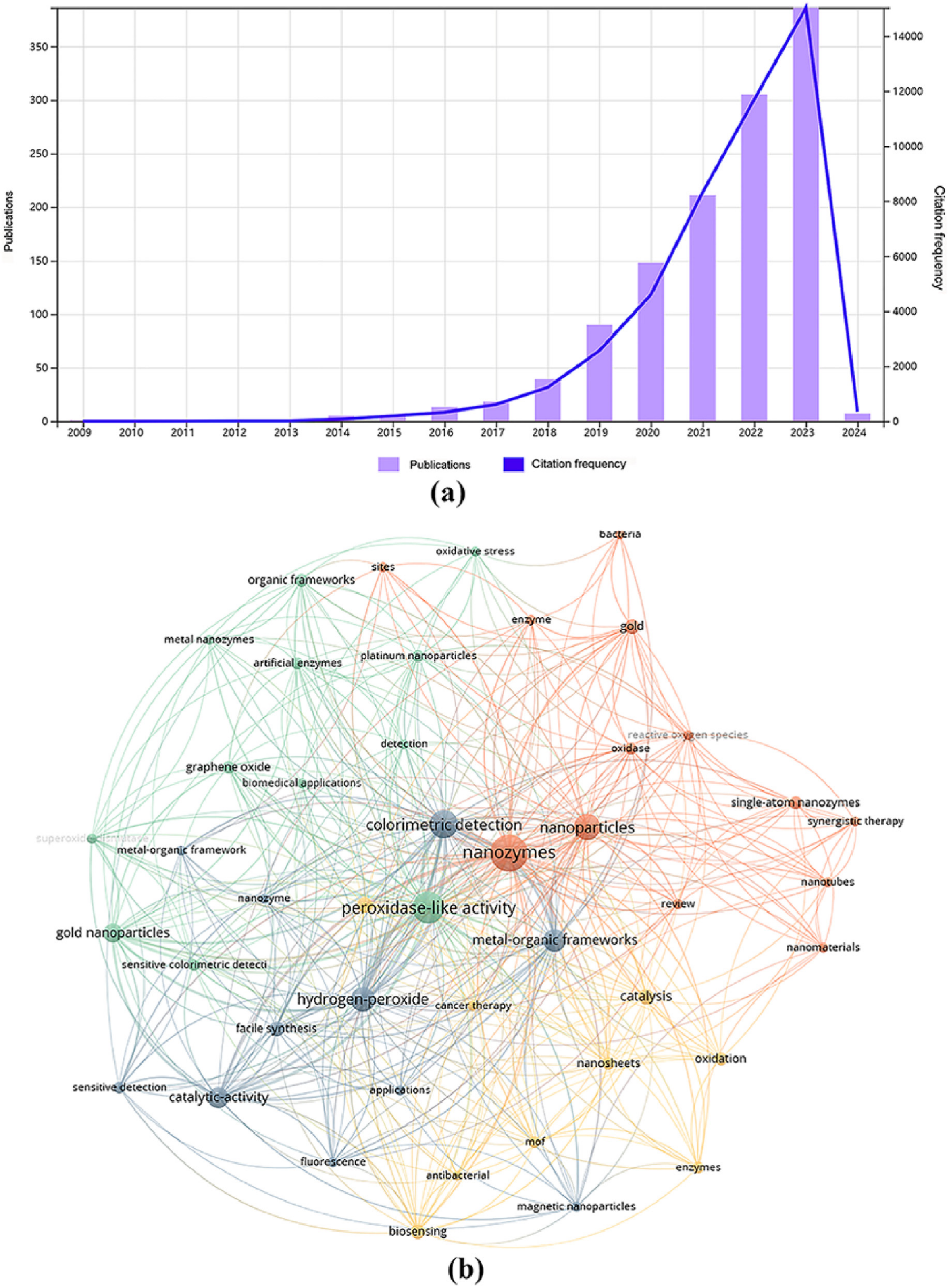


Fig. 1. (a) Publications and citation frequency on metallic nanozymes by March 2024. (b) Overlay visualization of metallic nanozymes co-occurrence analysis based on all keywords. Data were collected from the web of science. Node size indicates the number of documents.

significant attention in an effort to overcome the limitations of natural enzymes, hence increasing the study of bionic enzymes. The advent of "nanozymes" (nanomaterials with enzymatic catalytic capabilities) has broken this impasse and demonstrated significant research promise. The enzyme-mimicking characteristics of nanozymes permit them to efficiently catalyze substrates at mild physiological circumstances, yielding the same reaction products as natural enzymes [8]. Manea et al. [9] pioneered the notion of "nanozymes" by discovering the gold nanoparticles could simulate phosphodiesterase-like activity to catalyze the transphosphorylation reaction. Yan et al. [10] discovered in 2007 that Fe_3O_4 nanoparticles reveal interior peroxidase-like activity. Whereafter, the number of nanozymes investigations has grown exponentially (Fig. 1) [11–13]. Nanozymes outperform natural enzymes in terms of stability and repeatability, offering more opportunities for application [14–16].

The detection principle of nanozyme-based electrochemical sensors is mainly based on the electrochemical reaction generated by the target analytes adsorbed on the electrode surface, which realizes the transfer of electrons to generate electrochemical signals. Thus, the key to achieving high sensitivity and selectivity of the nanozyme-based electrochemical sensors is the superior electrocatalytic capabilities of the used nanozyme materials. Until now, metal nanoparticles [17–20], metal oxides [21–23], carbon materials [24–26] and hybrid-structured nanozymes (e.g., metal-organic frameworks) [27–29] have been discovered to express enzyme-mimicking activity. Metal nanoparticles have significantly more active sites on their surfaces due to the small particle size and high specific surface area, which make metal nanoparticles outperform other bulk phase materials in catalysis. Some metal nanoparticles (e.g., Au, Ag, Pt, Pd etc.) have been found to imitate the inherent enzymatic properties like those of natural enzymes because of their distinctive structural and electrical features [30,31]. The enzyme-like catalytic activity of metallic nanozymes is primarily produced via particle surface adsorption and fast electron transfer [32]. Meanwhile, the superior electrical conductivity of metallic nanozymes can effectively boost the electron transfer rate on the electrode surface, promoting the efficacy of the electrochemical biosensors. The outstanding biocompatibility of metal nanozymes, multiple enzyme activities and customizable microstructure also allow for the realization of the higher catalytic activity. Consequently, there are several research possibilities for electrochemical biosensing platforms based on metal nanozymes. The laborious immobilization procedure and inconsistent detection performance of enzyme-based sensors are successfully addressed by the application of metallic nanozyme-based sensors. In metallic nanozyme-based electrochemical biosensors, nanozymes typically serve as signal amplification tags for non-electroactive substances or electrocatalysts for electroactive substances to catalyze target analyte-specific reactions [33]. Combining the unique physicochemical properties of metallic nanozymes and flexible electrochemical detection methods, metallic nanozymes-based electrochemical biosensors have been widely implemented to determine biomarkers, such as biomolecules (glucose, uric acid, etc.), proteins, nucleic acids, bacteria and tumor markers [34–38].

The unique physical and chemical properties of metal nanoparticles make them ideal for the construction of efficient and sensitive electrochemical biosensors. However, metallic nanozymes still have the limitations of lower catalytic activity and selectivity with the comparison of natural enzymes. Combining theoretical calculations and simulations to deeply investigate the synthesis strategy and catalytic mechanism of metallic nanozymes can help to deepen the understanding of the structure-function relationship [39]. This offers theoretical direction for developing nanozymes with greater catalytic effectiveness. Despite numerous noteworthy reviews on nanozymes have been published, such

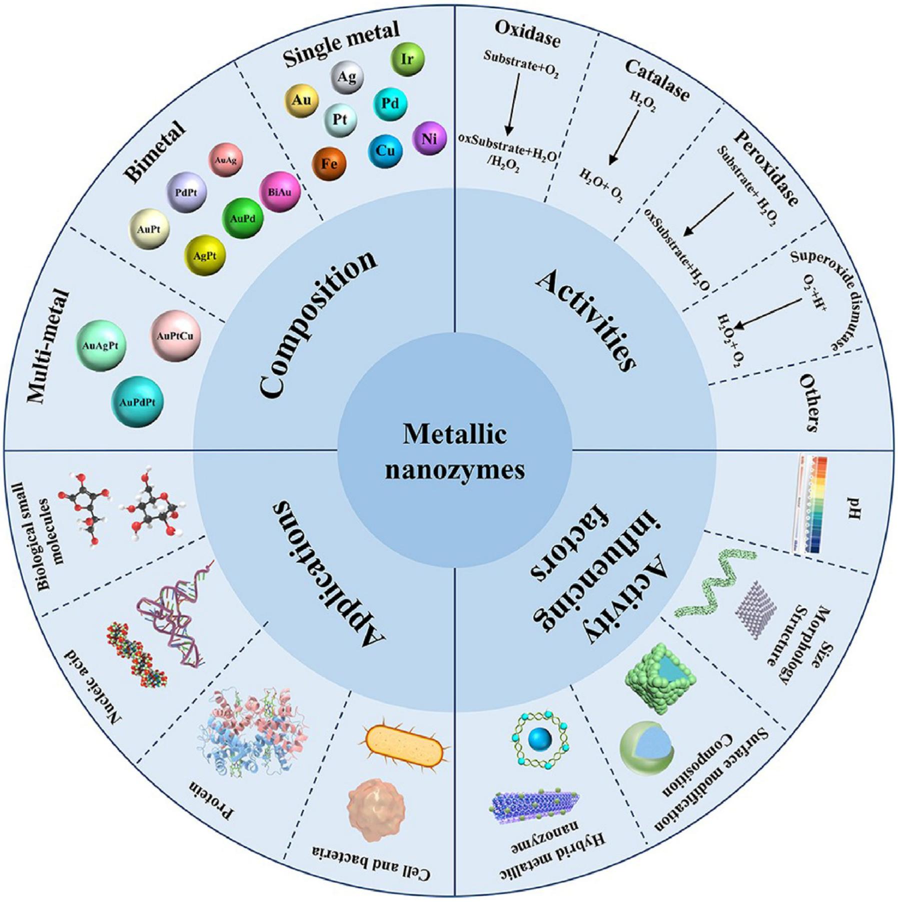


Fig. 2. Overview diagram: From the composition, activity, influencing factors and biological detection applications of metallic nanozymes to review.

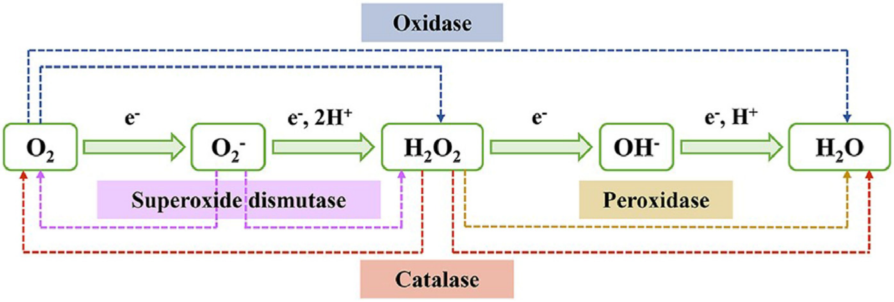


Fig. 3. Schematic diagram of a reaction catalyzed by enzymes.

as “Nanomaterials with enzyme-like characteristics (nanozymes): next-generation artificial enzymes (II)” and “Nanozymes: Classification, Catalytic Mechanisms, Activity Regulation, and Applications” [39–42]. These reviews have described the sensing applications of nanozymes, but there are fewer mentions of electrochemical sensing applications. There are fewer reviews that systematically introduce the application of metallic nanozymes in electrochemical biosensing. To help readers to understand more about the research progress of nanozymes in the field of electrochemical sensing, this paper focuses on the application of metallic nanozymes-based electrochemical sensors in the field of biomarker detection, and discusses the composition, the activity influencing factors and the catalytic mechanism of metallic nanozymes (Fig. 2). Additionally, it analyzes the existing difficulties and future potential of metallic nanozymes for electrochemical sensing applications. It is anticipated that more researchers will be drawn to create novel nanozymes materials with greater catalytic characteristics to promote further development of this field.

2. Classification of metallic nanozymes with electrochemical activity

Right now, metallic nanozymes have been more found to imitate oxidoreductase. The oxidoreductases catalyze substrates for redox processes, which include oxidase, peroxidase, catalase and superoxide dismutase. Considering that electrochemical biosensors rely more on the properties of redox metallic nanozymes, we concentrate on metallic nanozymes mimics of oxidase, peroxidase, catalase and superoxide dismutase (Fig. 3). Oxidases can catalyze the release of H_2O or H_2O_2 from the substrate in an atmosphere of O_2 [43]. O_2 is the electron acceptor during the oxidation of substrates catalyzed by oxidase-mimicking nanozymes [44]. Peroxidase oxidize the substrates utilizing hydrogen peroxide as the electron acceptor [45]. Inducing the breakdown of H_2O_2 into O_2 and H_2O by catalase helps to keep the amount of reactive oxygen species in the human body at an acceptable level [46]. The oxidative and antioxidant equilibrium of the human body depends on the antioxidant metalloenzyme superoxide dismutase (SOD), which induces the transformation of superoxide anion radicals (O^{2-}) producing O_2 and H_2O_2 [47]. At present, numerous studies have shown that Au, Pt, Pd and related alloy nanomaterials possess catalytic activity such as oxidase-mimicking, peroxidase-mimicking, catalase-mimicking and superoxide dismutase-mimicking enzymes [48–50]. The investigations on the catalytic mechanism of metallic nanozymes have also gained more and more attention [51–54]. Considerable advancements have been made in the sensing application of metallic nanozymes with the in-depth study of the catalytic process.

3. Metal materials for constructing metallic nanozymes with electrochemical activity

Currently, noble and transition group metal materials, such as Au, Ag, Pd, Pt, Fe, Ni, Mn and their alloy materials are the most widely studied metallic nanozymes materials [39,55]. To better comprehend their research progress, metallic nanozymes are categorized into monometallic, bimetallic, and polymetallic nanozymes in this paper (Table 1).

3.1. *Single metallic nanozymes*

The surface atoms of metal catalysts play a significant catalytic function for catalytic reaction pathways in which they are involved. As a significant electrocatalyst material, noble metal nanoparticles offer significant specific surface area, good electrical conductivity, and outstanding chemical stability, all of which are advantageous for the development of electrochemical sensors. The unfilled d electron orbital makes it simpler for reactants to adsorb on the surface of noble metal nanoparticle and produce intermediate active compounds, which exhibit remarkable catalytic activity. Many noble metals have been found to have inherent enzyme-like properties, with Au, Ag, Pt and Pd dominating the list [56–59]. Based on the unique electronic structure of noble metal nanoparticles, metallic nanozymes represented by Au, Pt and Pd can mimic various natural enzyme activities, such as glucose oxidase, peroxidase, catalase and so on. In addition, metallic nanozymes tend to exhibit great biocompatibility, which can maximize the protection of biomolecular activities. Noble metal materials are considered to be biologically inert, so they also have fewer toxic effects on living organisms, thus making them attractive for research in the biomedical field. Rossi et al., in 2004 discovered that gold nanoparticles could promote the aerobic oxidation of glucose to gluconate at mild circumstances and demonstrated impressive enzyme-like activity [60]. They then reported the specific mechanism of gold-catalyzed glucose oxidation in 2006 [61]. The primary mechanism of catalysis is the interplay of the hydrated glucose anion with gold atom to create the electron-rich gold, followed by nucleophilic attack on oxygen. The Au^{+}-O_2^{-} or Au^{2+}-O_2^{2-} electric couples act as the electron transfer bridge to facilitate the production of the final products, gluconate and H_2O_2. Jiang et al. [62] discovered that chitosan-stabilized AgNPs showed inherent peroxide-mimicking activity, which can catalyze the oxidation of TMB with the presence of H_2O_2. They verified the peroxide-mimicking activity by electron paramagnetic resonance (ESR) resulted from that H_2O_2 adsorbed on AgNPs surface can create ·OH radical. Kajita et al. reported that citric acid-reduced and pectin stabilized PtNPs (CP–Pt) can demonstrate catalase-like activity to breakdown H_2O_2 into O_2, while exhibiting superoxide dismutase-mimicking activity to quench O_2 [50]. The enzyme-like activity of noble metallic nanozymes makes them promising for use in biosensing systems for the detection and signal conversion of biomolecules. The enzyme-like activity of noble metallic nanozymes makes them promising for use in biosensing systems for the detection and signal conversion of biomolecules. Detailed sensing research work will be discussed and analyzed in Part 5 “Recent electrochemical biosensing applications of metallic nanozymes”.

Although noble metallic nanozymes exhibit amazing enzyme-like catalytic activity and high stability, their appeal in large-scale production and application is somewhat limited by the comparatively expensive cost of preparation. In recent years, transition group metals have

Table 1
Summary of references related to metallic nanozymes.

	Metal	Mimetic enzymatic activity	Nanozymes	Micromorphology	Ref.
Single metallic nanozymes	Au-based	Oxidase	MSN-Au	Nanoparticle	[85]
			CdS/ds-DNA/BSA/Au	Nanoparticle	[86]
			BSA-Au	Nanocluster	[87]
		Peroxidase	DAP-Au	Nanoparticle	[88]
			Au	Nanocluster	[89]
			MoS$_2$–Au	Nanoparticle	[90]
		Catalase	AuNFs/(PEI/PAA)$_{10}$/GR	Nanoflower	[91]
			Au–Si-ACD	Nanoparticle	[92]
		Superoxide dismutase	Au	Nanoparticle	[49]
	Ag-based	Oxidase	GQD/Ag	Nanoparticle	[26]
			BSA-Ag	Nanocluster	[93]
		Peroxidase	Ag-Mxene	Nanosheet	[94]
	Pt-based	Oxidase	Pt	Nanocluster	[95]
		Peroxidase	Pt DENs	Nanoparticle	[96]
			Pt	Nanocluster	[97]
			rGO-CNT/Pt	Nanoparticle	[98]
			Pt	Nanoparticle	[99]
		Catalase	Pt/COF	Nanoparticle	[100]
		Superoxide dismutase	Pt	Nanoparticle	[47]
	Pd-based	Oxidase	PdSP@rGO	Nanoplate	[101]
		Peroxidase	Pd	Nanoparticle	[102]
		Catalase	Pd	Nanocube	[103]
	Fe-based	Catalase	Fe–N$_4$	–	[104]
	Ir-based	Catalase	CD-Ir	Nanoparticle	[105]
	Ru-based	Peroxidase	Ru@GDYO	Nanoparticle	[106]
			Ru@G	Nanoparticle	[107]
			C$_3$N$_4$–Ru	Nanoparticle	[108]
	Rh-based	Peroxidase	Rh SAymes	Nanoparticle	[109]
		Oxidase	Rh SANs	Nanosheet	[110]
	Co-based	Peroxidase	Co-CD	Nanoparticle	[111]
Bimetallic nanozymes	AuPt-based	Oxidase	AuPt	Nanoparticle	[112]
			SDBA-PtAu/CNTs	Nanoparticle	[74]
			MoS$_2$–Au@Pt	Nanoparticle	[113]
		Peroxidase	Au@Pt	Nanoparticle	[114]
			Au@PtNP/GO	Nanoparticle	[115]
			Au@Pt	Nanorod	[116]
			Au@Pt	Nanoparticle	[117]
			Au@Pt	Nanoparticle	[118]
			Au/T15/Pt	Nano-bipyramid	[119]
		Catalase	Au@Pt	Nanoparticle	[118]
	AuAg-based	Peroxidase	Au@Ag	Nanorod	[17]
			Au@Ag	Nanorod	[120]
			AgAu-MWCNT	Nanoparticle	[121]
	AuNi-based	Oxidase	Au–Ni	Nanoparticle	[122]
	AuPd-based	Peroxidase	Au@Pd	Nanorod	[123]
		Catalase	AuPd-PDA	Nanoparticle	[75]
	AgPt-based	Peroxidase	FNA-Ag@Pt	Nanoparticle	[76]
Bimetallic nanozymes	AgPd-based	Peroxidase	AgPd@BSA/DOX	Nanoparticle	[124]
	AgCu-based	Peroxidase	Cu–Ag/rGO	Nanoparticle	[80]
	AgNi-based	Catalase	AgNiNP/RGO	Nanoparticle	[125]
	PtPd-based	Oxidase	Pt–Pd	Nanosuperlattice	[126]
			Pt–Pd/GO	Nanoparticle	[127]
		Catalase	PdPtNCs@SGN	Nanocluster	[128]
			PtPd@PCN-224	Nanoparticle	[129]
	PtCu-based	Oxidase	PtCu/MCNs	Nanoparticle	[130]
		Peroxidase	PtCu	Nanoframe	[79]
			PtCu$_3$	Nanocage	[78]
	PtIr-based	Oxidase	PVP/IrPt	Nanoparticle	[131]
	PtCo-based	Oxidase	PtCo	Nanoparticle	[132]
	PtNi-based	Oxidase	PtNi@AC	Nanoparticle	[133]
		Peroxidase	PtNi	Nanowire	[77]
	PtRu-based	Peroxidase	AMO-nPtRu	Nanoparticle	[134]
		Catalase	Ru/Pt@BSA	Nanoparticle	[135]
	PtBi-based	Peroxidase	BSA-Bi/Pt	Nanoparticle	[81]
	PdIr-based	Peroxidase/Catalase	Pd@Ir	Nanosheet	[136]
	PdCu-based	Peroxidase	CuPd@H–C$_3$N$_4$	Nanoparticle	[137]
			PdCu	Nanodendrite	[138]
	RuCu-based	Peroxidase/Catalase	RuCu	Nanoparticle	[139]
Polymetallic nanozymes	AuAgPt-based	Peroxidase	Au@Ag@Pt	Nanoparticle	[140]
		Catalase	Au@PtAg	Nanorod	[141]
	AuAgPd-based	Peroxidase	AuAgPd	Nanoparticle	[142]
	AuPtCu-based	Peroxidase	Au@PtCu	Nanorod	[143]
	PtPdRu-based	Peroxidase	PtPdRu	Nanorod	[84]
	PtPdIr-based	Peroxidase	PdPtIr	Nanoparticle	[83]

(continued on next page)

Table 1 (*continued*)

	Metal	Mimetic enzymatic activity	Nanozymes	Micromorphology	Ref.
Polymetallic nanozymes	PtPdCu-based	Oxidase/Peroxidase/Catalase	PtPdCu	Nanocube/Nanotetrahedron	[144]
	PdAgCu-based	Catalase	PdAgCu MNSs	Nanoparticle	[145]
	PtRhRuCu-based	Oxidase/Peroxidase	PtRhRuCu	Nanoparticle	[146]

attracted much attention due to their unique electronic structure leading to their valence variability, which makes them susceptible to redox reactions and conducive to promoting electrochemical processes [63,64]. It has been demonstrated that transition group metals (such as Ni, Co, Cu, Mn, Fe, etc.) possess similar catalytic activity and substrate affinity to natural enzymes, which have been widely used in the study of detection of biomolecules such as glucose and H_2O_2 [65]. Ni-based nanozymes are a class of metallic nanozymes that are currently being studied for electrochemical detection of glucose. This is due to the ability of Ni-based mimetic enzymes to form reaction intermediates (or transition states) with high catalytic activity under alkaline conditions, utilizing Ni^{2+}/Ni^{3+} redox pairs for electrochemical oxidation reactions with glucose [66]. Horseradish peroxidase (HRP), catalase, hemoglobin (Hb) and myoglobin (Mb) are the most commonly used reactive proteins for enzyme-based H_2O_2 sensors. Since the cofactor of these proteins, hemoglobin, uses Fe as the reactive site, Fe-based nanomaterials are considered to be the most potential material for H_2O_2 mimetic enzyme detection. Wei et al. synthesized monatomic iron-site-coupled carbon--encapsulated Fe_3C crystal nanozymes (Fe_3C@C/Fe–N–C) with intrinsic peroxidase activity for the electrochemical sensing of H_2O_2 [67]. Fe_3C@C/Fe–N–C demonstrated higher catalytic activity than traditional Fe–N–C due to the capacity of Fe_3C crystal to supply electrons to monatomic Fe. Mn is the active reaction center of many enzymes (e.g., catalase Mn-catalase) in living organisms. This has led to many Mn-based nano-enzymatic materials with peroxidase-like activity that can exhibit high reactivity in H_2O_2 electrochemical detection [68]. From the current research progress, high-entropy transition group metallic nanozymes, such as Ni, Mn, Fe, typically display peroxidase- and oxidase-like activities [69,70]. Therefore, transition group metallic nanozymes have lower catalytic ability than noble metallic nanozymes. And the research on their long-term safety is relatively lacking. The catalytic performance of transition group metallic nanozymes is promising to optimize by modifying their composition and structure.

3.2. Bimetallic nanozymes

Bimetallic nanomaterials are highly desirable as electrode modification materials due to their high electrocatalytic activity. Different atoms in the alloys create new binding sites or reaction pathways that can greatly affect the activation or binding energies of the reagents or intermediates, which may generate new reaction pathways and lower the reaction potential. Consequently, bimetallic nanomaterials typically display better physical and chemical properties compared with monometallic nanomaterials. The synergistic impact between each component metal nanoparticles can be also effectively improved by regulating the spatial arrangement of component atoms, which is anticipated to further boost the enzyme-like catalytic activity [71].

The exceptional catalytic activity of noble metal materials makes them highly desirable even with their expensive costs and rare reserves. Hence, numerous noble bimetallic nanozymes have been developed to obtain higher catalytic efficiency. In 2010, He et al. [72] prepared hollow/porous bimetallic AgM (M = Au, Pt, Pd) nanostructures by co-reducing Ag and M with ascorbic acid (AA) as the reducing agent. The AgM bimetallic nanostructures can rapidly accelerate the oxidation of horseradish peroxide (HRP) substrate. Then in 2011, He and colleagues created core-shell Au@Pt nanostructures by seed-mediated growing Pt nanodots on Au nanorods [73]. The produced Au@Pt core-shell nanostructures with extremely dispersibility displayed oxidase-, peroxidase- and catalase-mimicking activities, achieving the catalytic effect of TMB oxidation. The authors also investigated the implications of component ratio, pH, temperature and substrate concentration on the enzyme-mimicking of Au@Pt core-shell nanostructure. The experiment findings revealed that theses variables can effectively control the enzyme-like catalytic efficiency of the constructed Au@Pt core-shell bimetallic nanozyme. Wang et al. [74] designed and synthesized diboronic acid-modified PtAu/CNTs (SDBA-PtAu/CNTs) with oxidase-like activity for highly selective electrochemical monitoring of glucose. Liu et al. [75] prepared AuBP@Pt nanostructures and AuPd-PDA nanozymes for the detection of apolipoprotein E4, an important risk factor for Alzheimer (APOE4). Du et al. [76] used single-stranded nucleic acids as templates to quickly create tunable NA-Ag@Pt nanozymes. Based on this, functional nucleic acids (FNA) were modulated to create FNA-Ag@Pt nanozymes with peroxidase-like activity.

Reducing the cost of synthesis while enriching the diversity of the nanozymes and obtaining better properties is also a factor to be considered for the preparation of bimetallic nanozymes. Transition group metal materials are a desirable option due to their great catalytic activity. Zhu et al. [77] designed PtNi alloy nanowires according to the advantages of one-dimensional nanowire anisotropy and more crystal surface exposures. The produced PtNi alloy nanowires with a diameter of only 1 nm exhibited higher catalytic efficiency than that of natural HRP. The authors constructed a self-powered photoelectrochemical sensor utilizing PtNi alloy nanozymes as signal amplification tags in conjunction with interactions between biotin-streptavidin. The PtNi nanozymes-based sensor accomplished an extremely susceptible detection of chloramphenicol. Wang et al. [37] prepared AuCo ultrafine nanoparticles-modified hollow carbon framework (Au/Co@HCNF) nanozymes for the construction of electrochemical sensors for uric acid (UA). In this work, the nanozymes were made by pyrolyzing Au(III)-etched zeolite imidazolate backbone-67 precursor. Additionally, numerous kinds of bimetallic nanozyme materials, including PtCu nanocages [78], PtCu nanoframe [79], CuAgNPs [80] and Bi/Pt nanozyme [81] have been published.

3.3. Polymetallic nanozymes

The addition of multiple highly catalytically efficient metal elements to metallic nanozymes allows for the modulation of the electronic structure based on the synergistic interaction between the components. This strategy promises to customize the expressed enzyme-like activity, making polymetallic nanozymes considerable attractive and prospective for application. Zhang and his colleagues revealed the peroxides-mimicking activity of AgPt nanospheres and AgPd nanocrystals, and explored the usage of Pd in place of Ag to address the weakness of easy oxidation of Ag [20]. According to their earlier discoveries that Pd and Pt grow in an island-like pattern on Au nanorods [72,82], the authors expanded the approach to produce Pd/Pt alloy nanodots on Au nanorods. The synthesized Au@PdPt core-shell nanorods illustrated oxidase-mimicking activity to catalyze the oxidation of AA and TMB. He et al. created the trimetallic PdPtIr nanozymes, which resemble sea urchins, had a high susceptibility for H_2O_2 than the bimetallic Pd–Pt nanozymes [83]. The sea urchin-like structure helped trimetallic PdPtIr nanozymes exhibit superior peroxidase-mimicking activity and perform better in the detection of AA and H_2O_2. Li et al. [84] described a novel PdPtRu ternary metallic nanozyme for constructing an electrochemical sensor to detect SARs-COV-2 antigen. PdPtRu nanozyme demonstrated outstanding peroxidase-mimicking activity and proficient electrocatalytic activity against H_2O_2. The alteration of PdPtRu nanozyme on the electrode surface not only acted as a signal amplification catalytic tag, but also provided abundant active sites to fix and trap antibodies.

4. Regulating activity of metallic nanozymes for electrochemical biosensing

Despite the fact that metallic nanozymes have numerous benefits that are hard to match by natural enzymes, research on nanozymes has remained mostly at the laboratory stage up to now. This is mainly because, at this point, the specificity of metallic nanozymes cannot reach the level of natural enzymes, and the sensitivity and reproducibility need to be further improved. Therefore, it is essential to work toward enhancing the detection capabilities of metallic nanozyme-based electrochemical sensors to address the present issues and challenges. Metallic nanozymes are still considered nanomaterials by nature. Properties such as small size effect, quantum size effect, surface and interfacial effect, and macroscopic quantum tunneling effect are still applicable to them, which are expected to endow them with excellent catalytic properties. In addition, the catalytic mechanism of metallic nanozymes is different from that of natural enzymes that catalyze reactions with the help of proton transfer and acid-base co-catalysis, and the electron transfer process occurring on atom surface is the primary source of their catalytic activity [147]. Thus, functionalized design is considered to be an extremely effective way to improve the catalytic performance of metallic nanozymes. Specifically, it can be adopted as morphological structure modulation, size modulation, interfacial engineering, component modulation and hybrid metallic nanozyme construction. The external factors such as pH of the assay environment also have a vital impact on metallic nanozymes. These strategies for modulating the activity of metallic nanozymes will be discussed in this subsection.

4.1. pH

Like natural enzymes, the pH value of the surrounding environment has an influence on the catalytic activity of metallic nanozymes. Numerous metallic nanozymes possess the ability to imitate multiple enzyme activities, with the pH of the environmental medium acting as a “switch” (Fig. 4a) [48]. The investigations have demonstrated that neutral or alkaline environments motivate the production of catalase-mimicking activity and SOD-like activity, while acidic environments favor the expression of peroxidase-like activity [48,148]. In the case of AuNPs, Li and his colleagues theorized that the peroxidase-mimicking activity of AuNPs was primarily driven by the free radicals generated by H_2O_2 adhering to the AuNPs surface (Fig. 4b) [148]. They methodically investigated the impact of various pH values on the H_2O_2 breakdown caused by AuNPs. In a neutral environment, H_2O_2 adsorbed on the Au (111) surface can decompose in acid-like decomposition (H_2O_2 breaks the O–H bond to produce HO_2 and H) and base-like decomposition (H_2O_2 breaks the O–O bond to produce H_2O and O). The energy barrier for acid-like decomposition (1.60 eV) is higher than that for base-like decomposition (0.57 eV), which implies that H_2O_2 tends to undergo more base-like decomposition under neutral circumstances. Under acidic conditions, the energy barrier of H_2O and OH generated from pre-adsorbed H and H_2O_2 (0.61 eV) is higher that of base-like decomposition, indicating that H_2O_2 tends to undergo base-like decomposition and exhibits peroxidase-like activity. In contrast, H_2O_2 adsorbed on the Au (111) surface is more inclined to undergo acid-like decomposition, exhibiting catalase-mimicking activity. Xu and his co-workers revealed that Au NPs showed the best glucose-like oxidase at pH 6 and 65 °C, and Pt NPs showed the best catalase-mimicking activity at pH 7 and 55 °C (Fig. 4c) [149].

4.2. Size, faceting and crystal structure

Typically, when the particle size of nanomaterials reduces, the specific surface area will increase, the atomic exposure on the material surface will also greatly increase significantly, which means that materials will have more active reaction sites [68,150,151]. Thus, the nanomaterials size is well recognized to have a noticeable effect on their catalytic efficacy. For illustration, Luo et al. reported a self-limiting system resulting from the regulation of glucose oxidation product (gluconic acid)-induced surface passivation and size effects on AuNPs catalytic activity (Fig. 5a) [152]. Increasing particle size lowered the catalytic efficiency for glucose using varied sizes (13 nm, 20 nm, 30 nm and 50 nm) of Au NPs at the same concentration. Fu et al. [153] selected DNA (G-rich oligonucleotide AG22 and C-rich oligonucleotide RET2) as the template to synthesize Pt NPs. The authors chose K_2PtCl_4 and H_2PtCl_6 as the precursors to prepare Pt NPs with different sizes by regulating the molar ratio of precursors to DNA templates (1.7 nm to 2.9 nm). All prepared Pt NPs were shown to demonstrate peroxidase-like activity, however the original pace of the reaction slowed down as Pt NPs sizes shrank (Fig. 5b). This revealed that the particle dimension and the peroxidase-mimicking efficiency of Pt NPs were tightly correlated. Furthermore, the authors propose that the catalytic activity of the DNA-Pt is primarily derived from the Pt^0 component. In electrochemical sensing applications, the current response and detection sensitivity will be affected by the metal nanoparticle size [154–157]. Xu et al. [154] deposited various sizes AuNPs on graphene surface by varying the PVP graft density and utilized them for the electrochemical detection of L-cysteine (Fig. 5c). In the cyclic voltammetry analysis of L-cysteine, the oxidation peak intensity strengthened, and the peak position transformed negatively with the reduction of AuNPs particle size. In the electrochemical detection of H_2O_2 by PtNPs/graphene composite nanomaterials, Sun and his colleagues also found that the current responses and detection sensitivity significantly increased with the decreased PtNPs particle size [155]. Sonawane et al. [157] employed room temperature plasma-assisted technology to enhance the electrical characteristics of AuNPs. The AuNPs treated with plasma method had smaller particle size, which also showing higher sensitivity and linear fitting correlation in the electrochemically detecting cortisol (Fig. 5d). These investigations serve as more evidence that the catalytic activity of metallic nanozymes is intimately related to the exposure of the metal surface atoms.

When nanoparticles are exposed to different crystalline surfaces, molecules undergo adsorption and desorption behaviors on surface atoms with different energy barriers, which in turn affects their catalytic efficiency. Ge et al. [103] delved into the relationship regarding the surface energy of Pd nanocrystals with the activity of antioxidant enzymes by using electron spin resonance spectroscopy (Fig. 6a). The reaction energy of Pd (111) (2.81 eV) is higher than that of Pd (100) (2.64 eV), indicating that Pd (111) had superior H_2O_2 and O_2 scavenging activity than Pd (100). The catalytic activity of the nanozymes is also significantly affected by the crystal structure. According to the findings of in vitro tests, Pd octahedra exhibited stronger antioxidant enzyme activity than Pd cubes. Mazzotta et al. [158] presented octahedral Pt (111) capable of mimicking the enzyme-like glucose oxidase, with excellent sensing performance in the electrochemical detection of glucose (Fig. 6b). To demonstrate the influence of structural effects on electrocatalytic efficiency of PtNPs, they compared the electrochemical responses of the octahedral PtNPs to glucose with that of similarly nano-sized spherical PtNPs. The experiment results showed that the octahedral PtNPs had better sensing capabilities. These examples demonstrated that altering the crystal structure of the nanozymes can achieve modulation of the sensing performance.

4.3. Surface modification and composition

According to the hypothesis that the catalytic activity of metallic nanozymes is directly correlated with the electronic structure of metal elements, modifying the metallic nanozymes surfaces will have an impact on their catalytic efficiency. Numerous studies have demonstrated that controlling the types of surface functional groups and surface charge

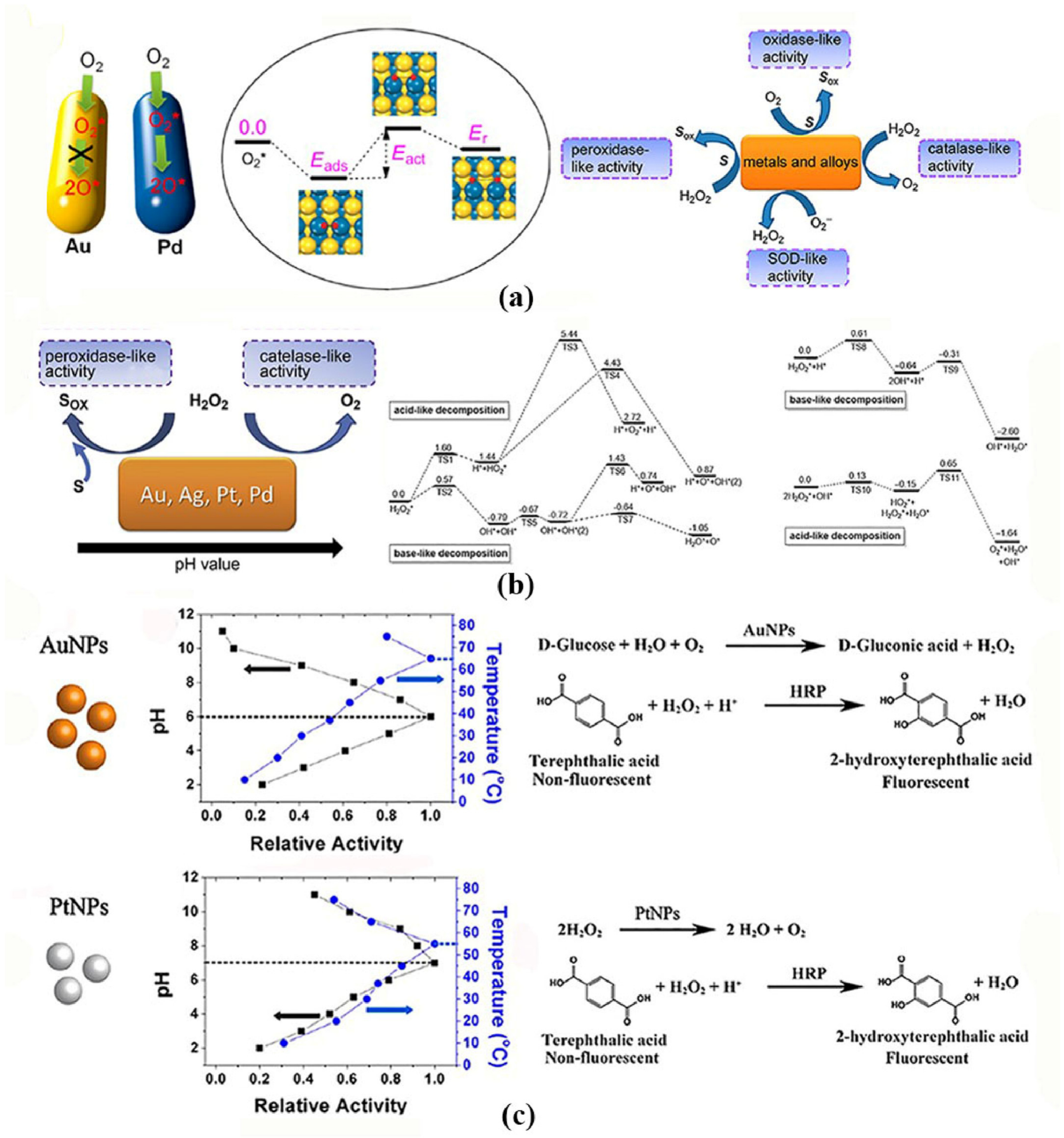


Fig. 4. (a) Enzyme mimetic activities of metals and alloys. S stands for organic substrates; Sox stands for oxidized organic substrates. Replicated with permission from Ref. [48] from American Chemical Society. (b) Calculated reaction energy profiles for H_2O_2 decomposition on the Au (111) surface in neutral, acidic and basic conditions. Replicated with permission from Ref. [148] from Elsevier. (c) The illustrations of reaction equations used to determine the activities and the pH activity and temperature activity profiles of Au NPs and Pt NPs. Replicated with permission from Ref. [149] from American Chemical Society.

characteristics can further enhance the catalytic activity, stability and selectivity of metallic nanozymes [88,159–163]. Modification of a charged ligand layer on the nanozyme surface can change the strength of the electrostatic interaction between the nanozyme and the substrate, which in turn affects the catalytic efficiency. Wang et al. [159] compared the catalytic efficiency of unmodified AuNPs (10 nm), amino-modified (30 nm) AuNPs and citrate-modified AuNPs (13 nm) using TMB as the oxidation substrates, and the results was as follows: unmodified AuNPs > citrate-modified AuNPs > amino-modified AuNPs. This was primarily because the citrate-modified AuNPs with negatively charged exhibited increased electrostatic attraction to TMB. Whereas, the amino-modified AuNPs with positively charged have reduced affinity for the positively charged TMB substrate. The inherent redox characteristics of citrate may affect the peroxidase-like activity of AuNPs.

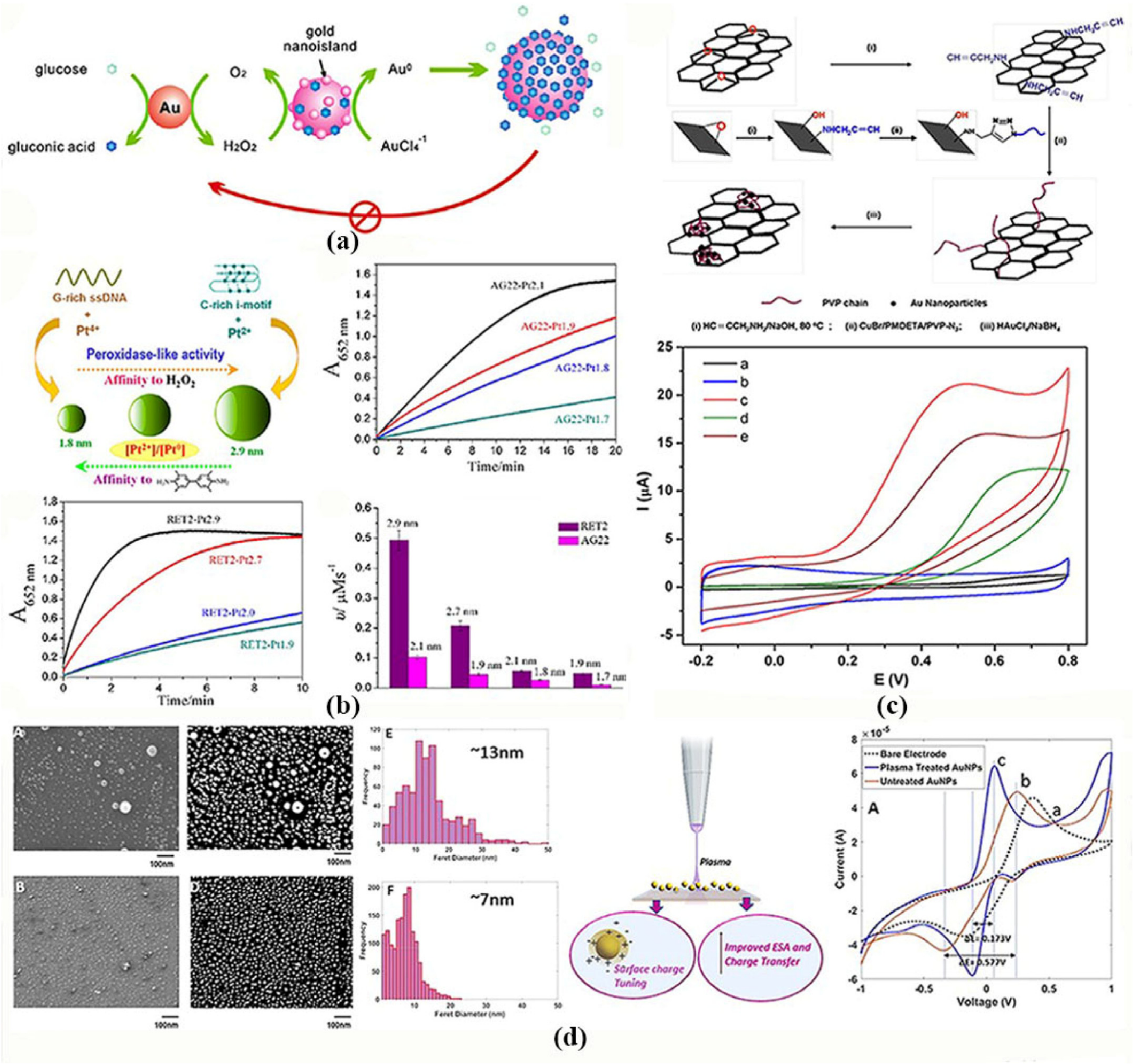


Fig. 5. (a) Schematic demonstration of the AuNP-based self-limiting growth system. Replicated with permission from Ref. [152] from American Chemical Society. (b) UV–vis absorption-time course curves of TMB-H_2O_2 reaction system (pH 4.0) catalyzed by different AG22-Pt and RET2-Pt at 25 °C; the initial velocities (V) of this reaction catalyzed by different DNA-Pt. Replicated with permission from Ref. [153] from American Chemical Society. (c) TEM of graphene-Au hybrid nanosheets with different particle size and different modified electrodes for detecting L-cysteine (c, graphene-Au_9) Replicated with permission from Ref. [154] from Elsevier. (d) Plasma-Induced Enhancement in Electronic Properties of Gold Nanoparticles (A-F in the reference picture is morphological features). Replicated with permission from Ref. [157] from American Chemical Society.

Modification of specific biomolecules on the nanozymes surface also can allow for the development of chemical structures that mimic the active sites of the enzymes. The group of Wu analyzed and compared the peroxidase activity of five purine-modified Au NPs mimics, of which 2, 6-Diaminopurine (DAP) capped Au NPs demonstrated the highest catalytic activity (Fig. 7a) [88]. Furthermore, the peroxidase-mimetic efficiency of AuNPs was dramatically boosted via the interaction between Fe^{2+} and purines. McVey et al. [161] modified casein on Au NPs surface to mimic peroxidase efficiency and promote the oxidation of TMB (Fig. 7b). The existence of casein not only significantly enhanced the intrinsic peroxidase activity but also served as a particular recognition cite, possessing enormous application potential. According to Nandhakumar et al. [162], when the redox pair $H_3N–BH_3$ (AB) is present, rapid catalytic hydrolysis of lipids can occur on the Pt NPs surface (Fig. 7c). Pt NPs would become electron-rich when the redox pair $H_3N–BH_3$ (AB) rapidly formed metal hydrides on their surface. This is a result of the easy generation of metal hybrids on Pt NPs in the presence of AB. The formation of metal hydrides conduces to electron-rich Pt NPs which assist the nucleophilic assault of H_2O on the carbonyl group of lipids and catalyze their hydrolysis. This characteristic made the electrochemical responses of Pt NPs nanozymes higher than that of natural enzymes. Pt NPs were utilized in association with AB to determine thyroid-stimulating hormone (TSH), exhibiting a low detection limit of 0.3 pg/mL.

The catalytic efficiency of metallic nanozymes catalysts can be

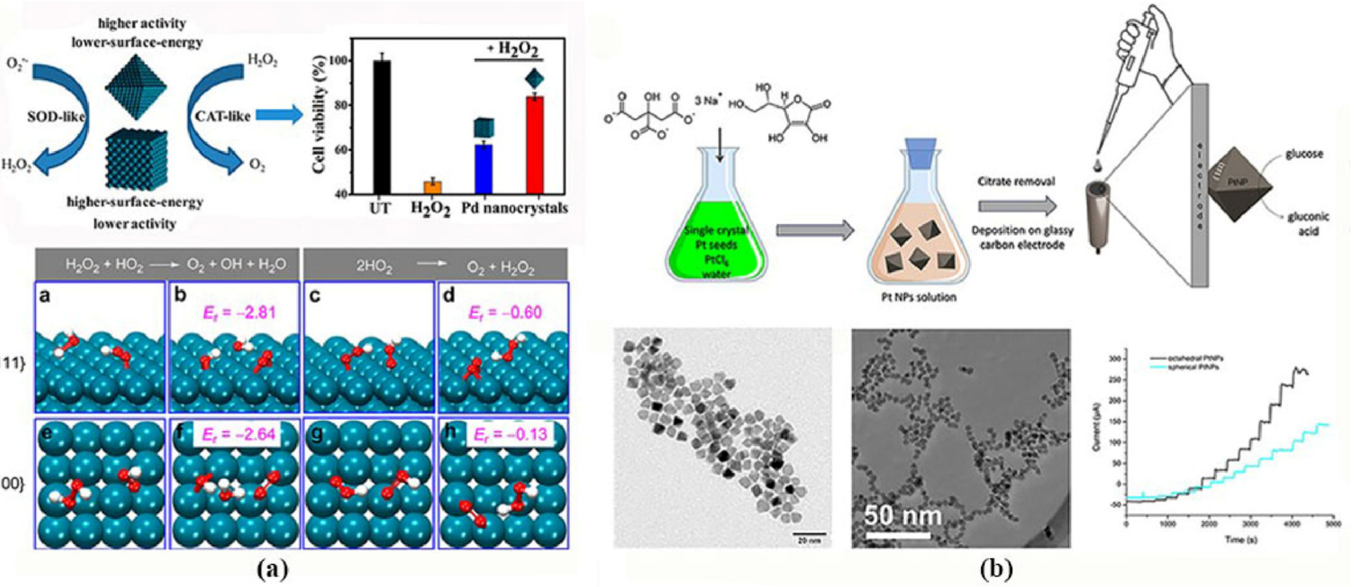


Fig. 6. (a) Different morphology of Pd nanocrystals with enzyme-like property. Lowest-energy adsorption structures and reaction energies (in eV) for the reactions on structures having either Pd (111) or (100) facets (a-h is the calculation result of adsorption energy of the corresponding crystal face in the reference picture). Replicated with permission from Ref. [103] from American Chemical Society. (b) Schematic representation of the synthesis protocol of octahedral Pt NPs and their use for glassy carbon electrode functionalization. BF-TEM images of octahedral 7 nm PtNPs and spherical 4 nm Pt NPs. Multiple Pulse Amperometric on 7 nm octahedral PtNPs (black curve) and 4 nm spherical/polycrystalline PtNPs (cyan curve). Replicated with permission from Ref. [158] from Springer.

regulated by introducing a second metal component to synthesize bimetallic nanozymes [89,164]. For example, the catalytic activity of Pt on glucose makes it a promising material for the construction of enzyme-free electrochemical glucose sensors. However, it is challenging to get strong Faraday currents for practical applications from the slow kinetically controlled glucose oxidation reaction at the Pt-based electrode. Researchers have prepared Pt-containing bimetallic nanozymes by doping additional metal components, such as Pt-Ni [5], Pt-Pd [165], and Pt–Au [166], which combined with synergistic interactions between the components improved the catalytic activity and stability. Niu et al. [165] reported the preparation of Pt–Pd nanoflakes with a three-dimensional structure using a template-free electrochemical deposition method. The glucose sensor featured a detection range of 0 mM to 16 mM and a detection sensitivity of 48 μA cm^{-2} mM^{-1}. Mahshid et al. synthesized Pt–Ni nanowire arrays using the template approach, which shows high electrocatalytic activity towards glucose in alkaline solution. Liang et al. [167] integrated the Co atomic site with Fe single atomic active site to develop FeCo bimetallic nanozymes Fe SAs/Co CNs (Fig. 8). The synergistic interaction of Fe and Co markedly boosted the peroxidase-mimicking activity and catalytic efficiency, additionally suppressing the aggregation phenomena and enhancing the electrical conductivity of nanomaterials. The experimental results also indicated that Fe SAs/Co CNs modified electrode interface has higher electron transfer efficiencies and better catalytic performance than Fe SAs. Adjusting the ratio of metal components in metallic nanozymes also allows for the modification of catalytic properties. Boujakhrout et al. [168] synthesized Au nanoparticles/Ag bipyridine hybrid nanomaterials to modulate the simulated peroxidase activity by controlling the Au/Ag ratio. With increasing AuNPs load, the electrocatalytic activity of Au/Ag nanozymes for reducing H_2O_2 grew, exhibiting higher reduction peak current signals and more negative potential values.

4.4. Hybrid metallic nanozyme

Designing hybrid nanozymes is an effective approach for enhancing their catalytic performance. Designing the support carriers of hybrid nanozymes into multilayer hierarchical structures is expected to improve the dispersion of metal nanoparticles and provide richer catalytic active sites. Introducing components with enzyme-like activity to compose the hybrid nanozymes is also an effective approach to improve the limited enzyme-like activity of the metallic nanozymes. Xu et al. [169] employed two-step electrodeposition to successively deposit GQDs and AuPd alloy nanoparticles on carbon fiber substrate (Fig. 9a). Compared with the single component modified electrode, the current density of the H_2O_2 reduction peak corresponding to the hybrid nanozymes modified electrode is significantly enhanced, and its peak position is positively shifted. It suggests that the structural advantages of the hybrid nanozymes composed of GODs and AuPd alloy nanoparticles, along with the synergistic effect between the components, can greatly enhance the electrocatalytic activity toward H_2O_2. Zhao et al. [170] described a graphene fiber (GF) microelectrode electrochemical sensing device that is functionalized utilizing hybrid nanozymes made of AuNPs encased in flower-like MnO_2 nanowires (MnO_2-NWs@Au-NPs) (Fig. 9b). The generated hybridized metallic nanozymes MnO_2-NWs@Au-NPs benefited from exceptional enzyme-like catalytic activities and distinctive hierarchical nanostructures, which exhibited superior electrocatalytic activity for H_2O_2 than single components. Wang et al. [171] inserted PdCu alloy nanoparticles in nitrogen-doped carbon nanofoam arrays, then modified them on flexible carbon fiber microelectrode (Fig. 9c). The porous structure of carrier not only made it possible to incorporate PdCu-ANPs at high density, but it also promoted mass transfer and diffusion processes during electrochemical reactions on the electrode surface. Based on the characteristics, the hybridized metallic nanozymes demonstrated remarkable electrochemical sensing performance for H_2O_2.

5. Recent electrochemical biosensing applications of metallic nanozymes

With the continuous development of advanced nanotechnology, the exceptional catalytic ability, durability and reusability of metallic nanozymes have contributed to a rapid growth in their potential to replace natural enzymes. These properties make metallic nanozymes a research focus in electrochemical sensing applications. In the field of biomolecular detection, there are two main types of detection principles in metallic nanozyme electrochemical sensors: metallic nanozyme

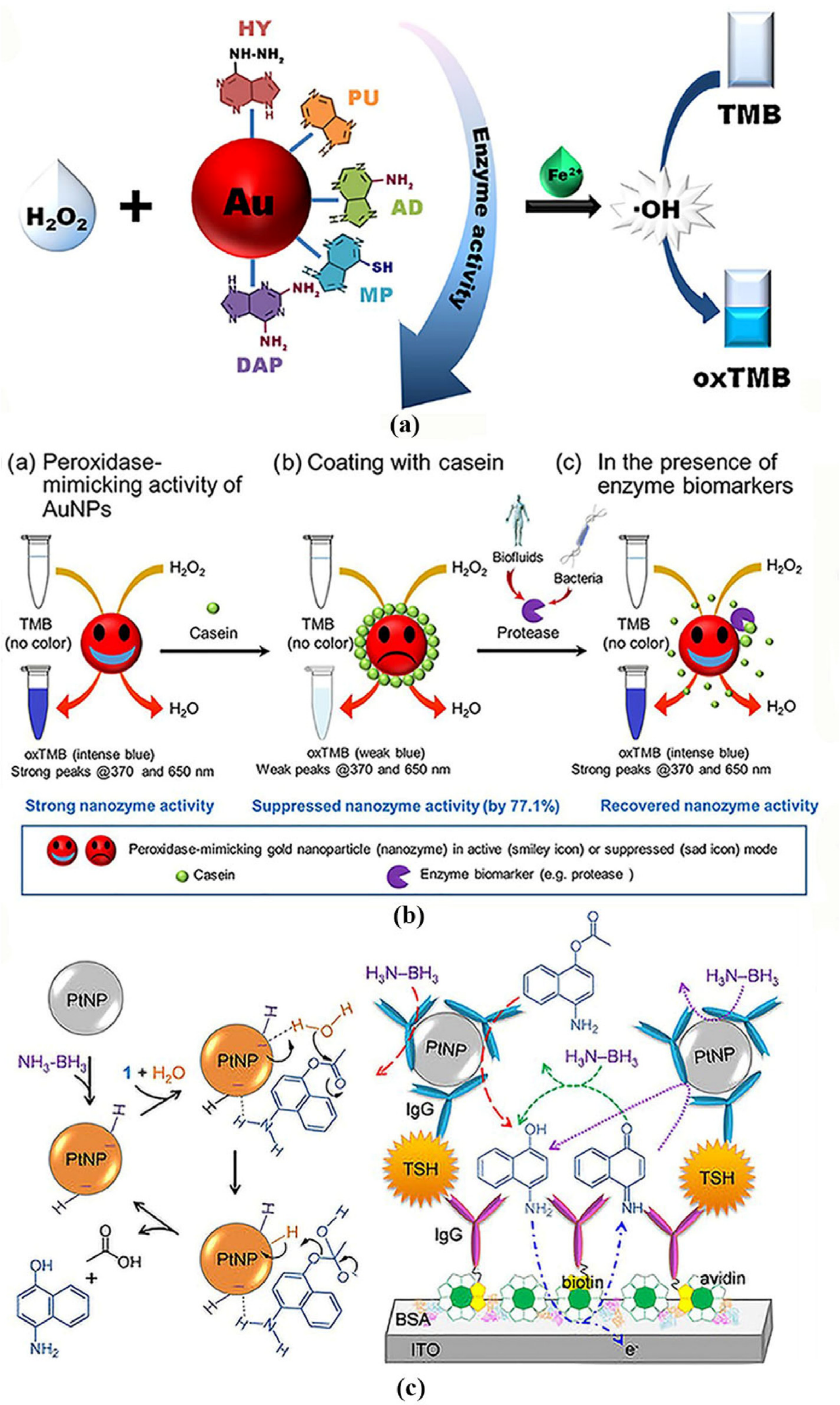


Fig. 7. (a) The molecular structure of purine derivatives and the peroxidase-like activity process of the AuNPs. Replicated with permission from Ref. [88] from Elsevier. (b) Overall scheme demonstrating the switching of peroxidase-mimicking activity of casein coated AuNPs for the detection of enzyme biomarkers ((a)–(c) in the reference picture are the expression of enzyme-like activities under different conditions). Replicated with permission from Ref. [161] from Springer Nature. (c) Suggested mechanism of the catalytic ester hydrolysis by Pt NPs and AB. Suggested mechanism of the catalytic ester hydrolysis by Pt NPs and AB. Replicated with permission from Ref. [162] from the Wiley-VCH.

recognizes the target analyte, reacting to produce recognizable electrochemical signals; metallic nanozyme acts as the signal tag to induce and catalyze reaction, amplifying the electrochemical reaction signal. The interaction between the modified electrode and the target analyte can produce changes in different types of electric signals such as current, potential and impedance. This further enhances the broad applicability of metallic nanozymes-based electrochemical sensors. Flexible electrochemical sensors have also been created to accommodate the need for continuous health monitoring, which is a significant advancement forward in the field of life and health. The convergence of innovation in metallic nanozyme materials and device paradigm shift will drive nanozyme-based electrochemical sensors towards real-life applications. Recent developments in metallic nanozymes-based electrochemical sensing platforms are analyzed and discussed below (Table 2).

Electrochemical sensors are typically based on a three-electrode operating system containing working electrode, reference electrode and counter electrode. The sensitive recognition layer is modified on the working electrode in the sensing system, which is the core part that is

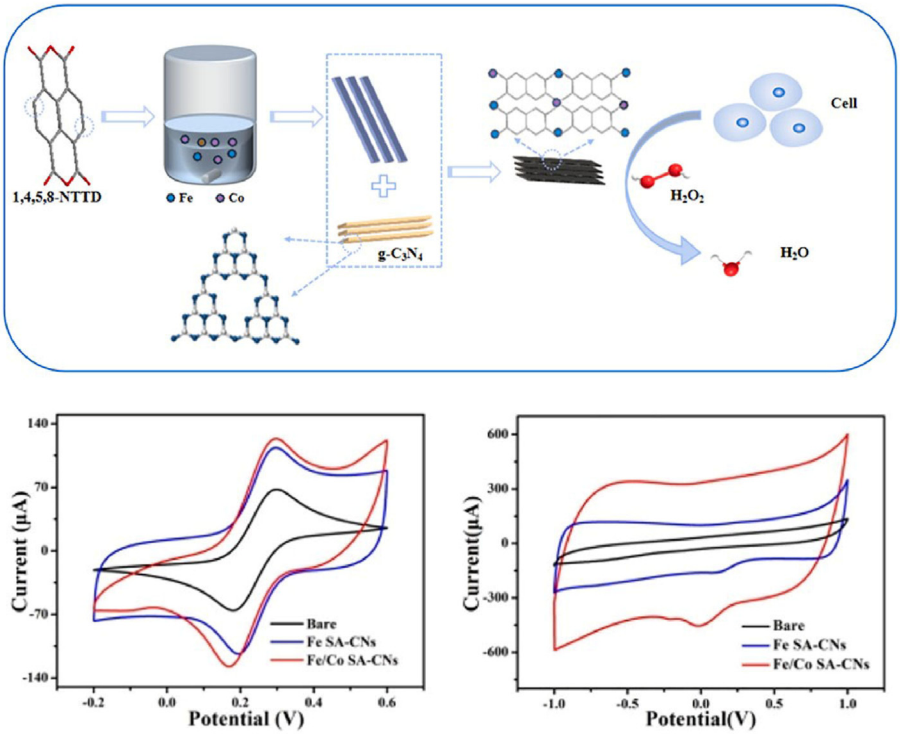


Fig. 8. Schematic Diagram of Real time Detection of H_2O_2 with Fe SAs/Co CNs. CV test for conductivity of two materials; CV test of two materials under 2.5 mM H_2O_2. Replicated with permission from Ref. [167] from Elsevier.

decisive for the sensing performance. Under the action of an applied voltage, the target analyte undergoes an electrochemical reaction on the modified electrode surface to produce an electrochemical response. The modification of metallic nanozymes on the surface of the working electrode enables highly sensitive and selective detection of the analytes. The metallic nanozymes-based electrochemical sensors have different analytical models for the detection of electrically active and non-electrically active substances, which will be discussed in detail in this section.

5.1. Metallic nanozymes as catalysts for recognition of target analytes

The human body produces a variety of small biological molecules, such as glucose, H_2O_2, lactic acid, uric acid and dopamine during physiological activities. These small biological molecules are essential for human metabolism and daily functions. An aberrant expression level of these little biological molecules will cause the body to malfunction, which will then induce the emergence of diseases. Therefore, accurate monitoring of the level of these small biological molecules is of great importance for preventive screening and diagnostic treatment of diseases. Metallic nanozymes often function as electrocatalysts in the electrochemical detection studies of small biomolecules mentioned above. The redox reaction of target analyte is catalyzed by the enzyme-like activity of metallic nanozymes under an applied voltage, which generates a corresponding electrochemical response. The concentration of target analyte and the generated electrochemical response are frequently associated, enabling quantitative investigation of the analyte. The high electrical conductivity and large specific surface area of metallic nanozyme can amplify the electrochemical signals in this process by increasing the rate of electron transfer between the target molecules and the electrodes. A few recent research results are selected to be discussed in this section.

5.1.1. Glucose

Glucose, one of the common monosaccharides, is the primary fuel of for living cells. Diabetes results in long-term harm and dysfunction to various body tissues and organs, which is harmful to human health. The prevention and treatment of diabetes benefit substantially from instantaneous blood glucose monitoring [211]. Considering the limitation of the limited enzyme-like catalytic activity of metallic nanozymes, the researchers tried to combine them with natural enzymes to form a cascade reaction to enhance the detection sensitivity [212]. Zhao et al. [178] prepared PbS colloidal quantum dots/Au nanospheres combined with GOx (PbS CQDs/AuNSs/GOx) for glucose detection (Fig. 10a). Based on the molecule-specific recognition function and signal amplification function of the modified layer, the detection limit of the device for glucose was as low as 1.432 nM.

Since GOx is still a biological protein by nature, changes in the environment can quickly alter its activity. The researchers modified the metallic nanozymes to achieve the equivalent catalytic activity as GOx to avoid the effects of unstable activity associated with the use of GOx. With the assistance of polydopamine (PDA), Xia et al. [172] by reduced and grew Au on the surface of porous anodized alumina oxide (AAO) nanochannels to synthesize the hybrid nanozyme Au-PDA-AAO. The produced Au-PDA-AAO nanochannels could sensitively sense the change in glucose concentration. Owing to the capable glucose oxidase-mimicking efficiency of Au NPs and the ion current amplification effect of AAO nanochannels, the Au-PDA-AAO nanozymes exhibited outstanding sensing performance with a determination limit of 0.2 μM. According to Fang and colleagues, $Au_{200}Bi$ aerogels have more glucose oxidation activity than Au aerogels, which was explained by the distinctive aerogel structure and the interaction of Au and Bi (Fig. 10b) [173]. The electrochemical sensor constructed based on $Au_{200}Bi$ aerogel had a linear range of 13 μM to 3.3 mM for glucose detection, a detection limit of 8.7 μM and a sensitivity of 664 $\mu A\ mM^{-1}\ cm^{-2}$. Wei et al. [130] constructed a nanozyme electrochemical sensor by embedding PtCu alloy nanoparticles on mesoporous carbon nanospheres (PtCu/MCNs) via electrostatic adsorption (Fig. 10c). Among them, PtCu/MCNs (1:1) had the highest electrocatalytic activity for glucose oxidation and excellent performance in glucose detection in beverages. Liu et al. [177] prepared

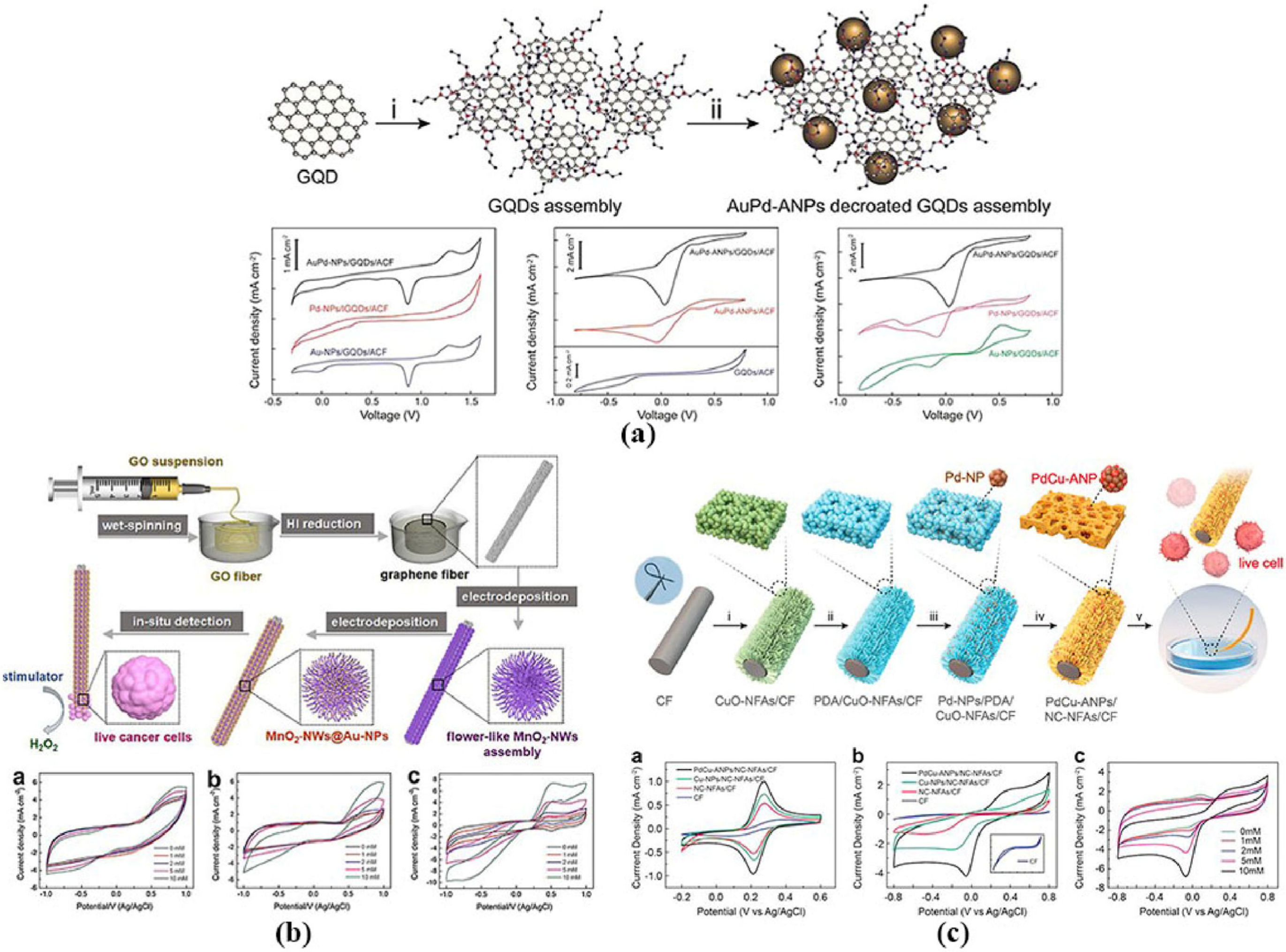


Fig. 9. (a) Schematic illustration of the formation of GQDs assembly and AuPd-ANPs decorated GQDs assembly. CV curves of different modified microelectrodes in 0.5 M H_2SO_4. CV curves of different modified microelectrodes in 0.1 M PBS solution containing 5 mM H_2O_2. Replicated with permission from Ref. [169] from Elsevier. (b) Schematic illustration of the fabrication procedure of MnO_2-NWs@Au-NPs/GF microelectrode for live cells detection. CV curves MnO_2-NSs/GF, MnO_2-NWs/GF and MnO_2-NWs@Au-NPs/GF microelectrodes in 0.1 M N_2-saturated PBS (pH 7.4) containing 0 mM, 1 mM, 2 mM, 5 mM and 10 mM H_2O_2. Replicated with permission from Ref. [170] Elsevier. (c) Schematic illustration of the fabrication procedure of PdCu-ANPs/NC-NFAs/CF. CV curves of different modified microelectrodes in 0.1 M KCl solution containing 1.0 mM $Fe(CN)_6^{3-/4-}$ and 0.1 M PBS solution containing 5 mM H_2O_2. CV curves of PdCu-ANPs/NC-NFAs/CF microelectrode in 0.1 M PBS solution containing 0 mM, 1 mM, 2 mM, 5 mM and 10 mM H_2O_2. Replicated with permission from Ref. [171] from Elsevier.

N-doped carbon nanostructures by pyrolysis of ZIF-8 as a precursor and successfully prepared amorphous Ni/Co bimetallic nanoparticles on carbon cloth substrates (a-Ni_2/Co_1-NC/CC) (Fig. 10d). The introduction of Ni enhanced the electrocatalytic sensitivity towards glucose; the addition of Co reduced oxidation potential of glucose and increased the selectivity towards glucose. Based on the synergistic catalytic effect between Ni and Co, the increased electron transfer efficiency of a-Ni_2/Co_1-NC/CC boosted the catalytic performance towards glucose. Interestingly, a-Ni_2/Co_1-NC/CC demonstrated better electrocatalytic activity than crystalline-Ni_2/Co_1NPs/CC. This was attributed to the large specific surface area of NC that increased the proton diffusion rate in the reaction system. Zheng et al. [179] concentrated on the application of Bi-based materials for glucose electrochemical sensing (Fig. 10e). The Bi(III)/Bi(V) redox cycle on the surface of Bi NPs prepared by laser ablation was the main source of catalytic activity towards glucose. The authors chose Ni or Co for surface doping of Bi NPs, which increased the transition group metal active sites and effectively enhanced the detection performance of glucose.

Academia and industry have been working on the development of electrochemical sensors with high sensitivity and selectivity to ensure that they exhibit reliable accuracy despite complex backgrounds. Nowadays, automation, intelligence, and high-tech internet have emerged as the new directions for sensor development in the current climate of rapid technological advancement. The rise in popularity of wireless communication, electronic technology, and seamless sensor connections—especially in light of the global information wave-further encourages the development of sensors that are better suited for use with smart wearable devices, thereby enabling accurate, real-time monitoring. Point-of-care test (POCT) has become one of the current trendsetters in the development of in vitro molecular diagnostics due to its simplicity, rapidity, portability, and lack of site constraints. Ideally, POCT-based sensor analyzes target analytes in biological samples in a short period of time through simple manipulation and provides rapid results. The introduction of metallic nanozymes into the construction of POCT-based sensors is an attempt by researchers to enhance the performance of devices for adapting the complex operating environments. A series of research results have also shown that metallic nanozymes-based POCT devices can realize high-performance sensing detection [213].

In fact, the original purpose of POCT devices was to track urine and blood sugar levels in diabetic patients. Glucose meter typically uses

Table 2
Summarization of electrochemical sensors based on the metallic nanozymes.

Analytes	Metallic nanozymes	LOD	Sensitivity	Linear Range	Ref.
Glucose	PtPd BMNSLs	1 μM	–	1 μM to 500 μM	[126]
	PtCu/MCNs	0.000 5 μM	574.1 μA mM^{-1} cm^{-2}	0.001 mM to 5 mM	[130]
	PtNi@AC	0.052 μM	–	0.1 mM to 1 mM, 25 μM to 1.25 mM	[133]
	Au-PDA-AAO	0.2 μM	–	0.5 μM to 50 μM	[172]
	Au$_{200}$Bi	8.7 μM	664 μA mM^{-1} cm^{-2}	13 μM to 3.3 mM	[173]
	Pt NPs	29.15 μM	3.43 μA mM^{-1} cm^{-2}	0 mM to 1 mM	[174]
	AuNP-MIP	1.25 nM	–	1.25 nM to 320 nM	[175]
	Au nanopine needles	7 μM	–	25 μM to 250 μM	[176]
	a-Ni$_2$/Co$_1$-NC/CC	0.15 μM	2 455 μA mM^{-1} cm^{-2} 1 300 μA mM^{-1} cm^{-2}	0.002 mM to 2 mM, 2 mM to 6 mM	[177]
	PbS/CQDs/AuNSs/GOx	0.001 432 μM	238 μA mM^{-1} cm^{-2}	0.000 1 mM to 10 mM	[178]
	Bi NPs	19.9 μM	127 μA mM^{-1} cm^{-2}	20 μM to 2 300 μM	[179]
	Ni–Bi NPs	1 μM	677 μA mM^{-1} cm^{-2}	1 μM to 3 500 μM	
	Co–Bi NPs	4 μM	2 326 μA mM^{-1} cm^{-2}	1 μM to 3 500 μM	
	rGO/PU-Au nanohybrid wrinkled	0.5 nM	–	0.5 nM to 10 mM	[180]
	Nanoporous gold	0.01 mM	253.4 μA mM^{-1} cm^{-2}	0.01 mM to 1 mM	[181]
H_2O_2	PtNP/rGO–CNT/PtNP	4.3 μM	206 μA μM^{-1} cm^{-2}	25 μM to 1 000 μM	[98]
	Au@PtNP/GO microbeads	1.62 μM	–	1 μM to 3 mM	[115]
	AgNiNP/RGO	0.9 μM	3 538.6 μA mM^{-1} cm^{-2}	0.003 mM to 13 mM	[125]
	Pt–Pd NPs/GO-CFMs	0.3 μM	–	1 μM to 35 μM	[127]
	AuNPs-NH$_2$/Cu-MOF	1.2 μM	1.71 μA μM^{-1} cm^{-2}	5 μM to 850 μM	[182]
	Pt/CeO2/NCNFs	0.049 μM	185.6 μA mM^{-1} cm^{-2}	0.000 5 μM to 15 mM	[183]
	Ag/2D Zn-MOF	1.67 μM	–	5.0 μM to 70 mM	[184]
	Pd/Au thin film	0.08 nM	–	0.1 nM to 333.3 μM	[185]
	Co–N–C/rGA	0.74 μM	–	3 μM to 2 991 μM	[36]
	AuNPs/NPC	0.067 μM	–	0.2 μM to 1 000 μM 1 000 μM to 7 000 μM	[186]
	CuSAN	2.087 μM	130.0 μA μM^{-1} cm^{-2}	0.003 mM to 0.91 mM	[187]
Uric acid	Au/Co@HNCF	0.023 μM	–	0.1 μM to 2 500 μM	[37]
	CuNPs/CN	–	0.52 μA μM^{-1} cm^{-2}	0.03 μM to 175 μM	[188]
	Au/Ni-MOF	5.6 μM	–	15 μM to 500 μM	[189]
	GP5AuNPs5	1.47 μM	0.23 μA μM^{-1} cm^{-2}	20 μM to 500 μM	[190]
	Fe/BNC	0.28 μM	–	0.5 μM to 2 065 μM	[191]
	FeSAs	1 μM	–	1 μM to 425 μM	[192]
Uric acid	Co–N–C/rGA	0.53 μM	–	2 μM to 45 μM	[36]
Dopamine	CuNPs/CN	–	1.03 μA μM^{-1} cm^{-2}	0.015 μM to 140 μM	[188]
	GP5AuNPs5	0.01 μM	18.7 μA μM^{-1} cm^{-2} 1.56 μA μM^{-1} cm^{-2}	0.02 μM to 0.16 μM 0.76 μM to 40.76 μM	[190]
	Fe/BNC	0.8 μM	–	1 μM to 630 μM	[191]
	Co-BNCNTs	0.034 2 μM	–	0.5 μM to 150 μM	[193]
	Co–N–C/rGA	19.38 μM	–	5 μM to 300 μM	[36]
Catechol	Co-AcNC-3	0.072 μM	-	4 μM to 300 μM	[194]
miRNA-21	H0@AuPtNPs	84.1 fM	-	10 fM to 1 nM	[195]
HULC	cDNA@AgNPs@LB@AuE	0.42 fM	–	1 fM to 500 fM	[196]
cfDNA(KRAS)	PCNs@AuPdCe	84 aM	–	1 fM to 1 nM	[197]
Human epidermal growth factor receptor 2	FeNC	4.5 pg/mL	–	0.01 ng/mL to 50 ng/mL	[198]
Matrix metallopro-teinase-2	Au@Pt NRs	0.18 ng/mL	–	0.5 ng/mL to 100 ng/mL	[116]
Thyroid-stimulating hormone	PtNP-IgG	0.3 pg/mL	–	0.3 pg/mL to 1 μg/mL	[162]
Prostate specific antigen	Au/NPC/PdAgCu MNSs	0.003 3 pg/mL	–	0.000 01 ng/mL to 100 ng/mL	[199]
	AuNP/peptide-Cu^{2+}	0.40 pg/mL	–	1.00 pg/mL to 5.00 × 10^2 pg/mL	[200]
Heart-fatty acid binding protein	MIP-NMIs-ERGO/ITO(Au)	2.29 fg/mL	1.34 × 10^{13} μA mM^{-1}	1 fg/mL to 100 ng/mL	[201]
Recombinant osteoprotegerin protein	AuAgPt	1.81 pg/mL	–	0.1 fg/mL to 10 ng/mL	[202]
Cortisol	Au single-atom nanozymes	0.48 pg/mL	–	0.15 ng/mL to 300 ng/mL	[203]
Neuron specific enolase	rGO/Thi/AuPt NAs	0.03 pg/mL	–	0.000 1 ng/mL to 50.0 ng/mL	[204]
Vascular endothelial factor	PdPtMo NPs	8.2 pg/mL	–	10 pg/mL to 1 μg/mL	[205]
MCF-7	Apt/Au@PbMo	2 cells/mL	–	2-1 × 10^5 cells/mL	[206]
MCF-7	AuIrPt	2 cells/mL	–	5-1 × 10^6 cells/mL	[207]
MCF-7	Pd–Ir CNE	2 cells/mL	–	10-1 × 10^6 cells/mL	[208]
Burkholderia pseudomallei	PtPd@PCN-224	12.8 aM	–	100 aM to 10 nM	[123]
Pseudomonas aeruginosa	AuNPs	60.0 CFU/mL	–	60-6.0 × 10^7 CFU/mL	[209]
Staphylococcus aureus	Au@Fc-Apt	10 CFU/mL	–	10–10^5 CFU/mL	[210]

fingertip blood glucose monitoring to determine blood glucose at the moment of sampling. The principle of measurement is mainly based on an electrochemical reaction generated by the enzyme glucose oxidase immobilized on the sensor, which is processed by data collection and algorithms to convert the electrical signal into glucose concentration. Considering the potential risk of infection and the pain caused to patients by blood sample collection, the researchers attempted to use bodily fluids such as perspiration, saliva, tears, and tissue fluids as test samples. The construction of portable non-invasive monitoring glucose sensing system will be the mainstream trend of future development. Research has indicated a connection between blood glucose levels and sweat glucose levels [214]. Numerous noninvasive electrochemical flexible sweat sensors were developed to replace sensor intrusive sensors [215–217]. However, the majority of transition group metal-based electrochemical glucose sensors function best in alkaline environments (pH > 11). These sensors tend to exhibit poor performance in near-neutral human sweat environments. Furthermore, friction between the sensor and the skin may damage the catalytic layer, resulting in degraded device performance. Sweat collection and processing is also one of the important factors affecting the accuracy of glucose content detection. The selection

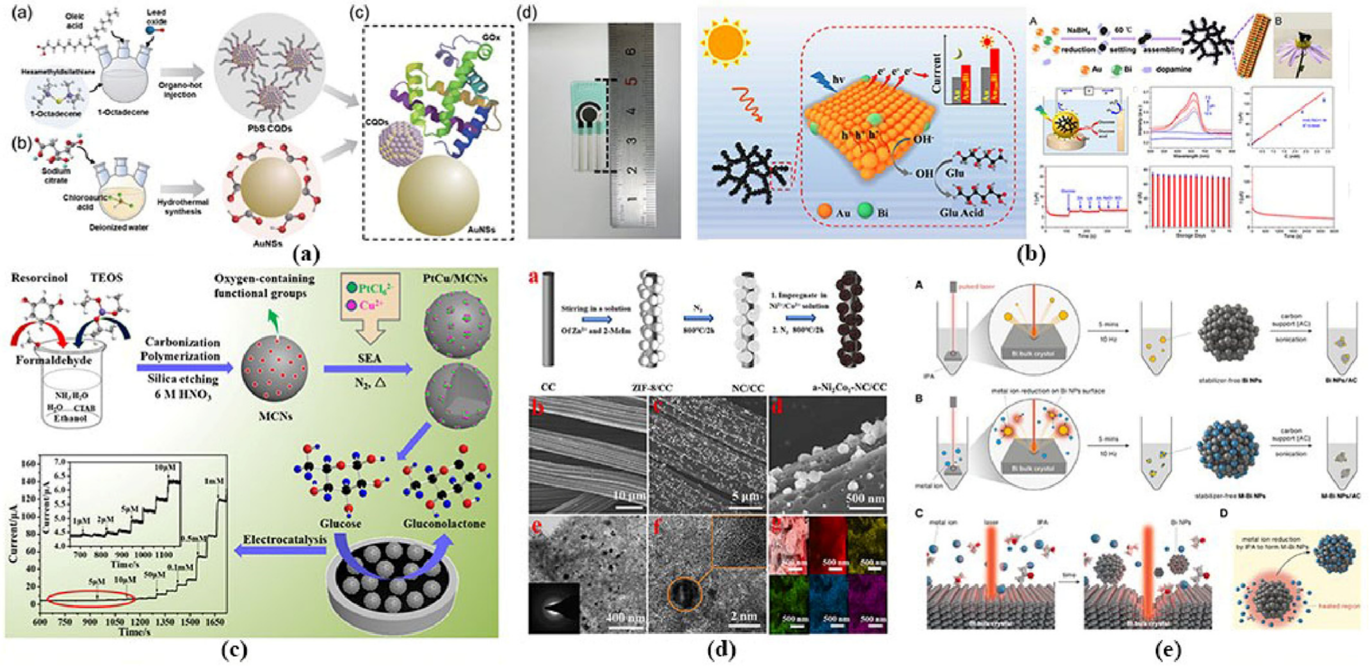


Fig. 10. (a) Preparation processes of PbS CQDs/AuNSs/GOx electrochemical biosensor ((a) to (d) in the reference picture are the nanozyme preparation process and the optical pictures of sensor). Replicated with permission from Ref. [178] from Springer. (b) $Au_{200}Bi$ aerogels for enhanced nonenzymatic electrochemical glucose sensing(A and B in the reference picture are schematic illustration of the preparation of $Au_{200}Bi$ hydrogels). Replicated with permission from Ref. [173] from American Chemical Society. (c) Schematic illustration of the preparation of PtCu/MCNs for glucose detection. Replicated with permission from Ref. [130] from Springer. (d) Scheme of a-Ni_2/Co_1-NC preparation on carbon cloth (a is scheme of a-Ni_2/Co_1-NC preparation on carbon cloth, and b-g are morphology characterization of a-Ni_2/Co_1-NC). Replicated with permission from Ref. [177] from Elsevier. (e) Illustration of the laser-assisted synthetic process of Bi NPs/AC and M − Bi NPs/AC (M = Ni or Co) composites (A-C in the reference figure are illustration of the laser-assisted synthetic process). Replicated with permission from Ref. [179] from Elsevier.

of materials for the sensitive layer and the design of the sweat collection structure of the flexible sweat electrochemical glucose sensor are two key challenges that need to be overcome.

Li et al. [174] created a wearable sweat glucose electrochemical sensor employing Pt/MXene nanocomposite for non-invasive ongoing glucose surveillance (Fig. 11a). The Pt/MXene nanocomposite showed a wide linear detection range (0 mM to 1 mM) and high sensitivity (3.43 $\mu A\ mM^{-1}\ cm^{-2}$) at neutral environment. To minimize the loss to the catalytic layer resulting from friction between the skin and the sensor, the authors created conductive hydrogels (CH) made of polyvinyl alcohol and MXene to immobilize Pt/MXene. This strategy significantly increases the stability of catalyst, thus extending the lifetime of the sensor. The microfluidic patches with storage were designed for skin sweat collection. The function of the microfluidic patch structure is to lessen the disturbance that perspiration collecting causes to the detecting process. There were no significantly change in the detection current signals in the anti-interference experiment with the presence of common physiological molecules. Additionally, the determined current values of flexible sensor for various glucose concentrations changed within 3 % of the initial values after 100 bends, indicating that the device proved outstanding flexibility stability. In an in vitro sweat assay experiment, the authors measured the glucose levels in the sweat of volunteers throughout the day using the Pt/MXene-based sensor. The assay results showed similar trends compared with commercial glucose meters. Toi et al. [180] created an enzyme-free electrochemical sensing platform based on Au-covered reduced graphene oxide/polyurethane composite fibers (WSNF) for the quantitative detection of glucose in sweat (Fig. 11b). The synergistic interaction between Au nano-wrinkles and rGO carriers promotes the oxidative dehydrogenation step of glucose. The authors combined the WSNF sensing patch with a stretchable fabric to achieve continuous monitoring of glucose levels in human sweat. Bae et al. [181] created an integrated sweat glucose sensor made of a flexible passive microfluidic and a stretchable nanoporous gold electrochemical sensor (Fig. 11c). Stretchable cotton fabric was inserted into the electrode channel to serve as a capillary, collecting and passively transferring perspiration from the skin to the electrode surface for the purpose of continuous monitoring.

5.1.2. H_2O_2

The most prevalent active oxygen molecule in living cells is H_2O_2, which is a byproduct of active oxygen metabolism. H_2O_2 and cell growth and death are tightly connected. Various metallic nanozymes mimicking peroxidase activity have been administered in electrochemical sensing platform applications for determining H_2O_2 [115,218–221]. Guan et al. employed N-doped carbon nanofibers as a matrix loaded with Pt/CeO_2 (Pt/CeO_2/NCFs) nanozymes and dramatically increased the structural stability as well as the electrocatalytic activity of the composites towards H_2O_2 [183]. The device presented a low detection limit (0.049 μM), a broad linear range (from 0.000 5 mM to 15 mM) and great sensitivity (185.6 $\mu A\ mM^{-1}\ cm^{-2}$) in electrochemical analysis and determination. Moreover, it also had a high accuracy in the determination of H_2O_2 in cosmetics. As described by the authors, the following explanations explain the improved sensing performance: the enhanced dispersion of Pt nanoparticles by CeO_2 nanoplates can drastically enhance the mimicking catalase efficiency of the nanozymes; the embedded structure of the Pt/CeO_2/NCFs nanocomposites and the three components worked together synergistically to create more active reaction sites.

Metal-organic framework (MOF) with high porosity and excellent chemical stability also serves as an ideal support material for metallic nanozymes. Chen et al. [184] prepared two structures (nanosheets and dodecahedra) of Zn-based MOFs and utilized electrodeposition to load Ag NPs on their surfaces to construct electrochemical sensors for the quantitative analysis of H_2O_2 (Fig. 12a). The snowflake-like Ag nanoparticles with high surface area and favorable dispersion were produced on two-dimensional (2D) Zn-MOFs nanosheets surface, whereas Ag NPs on three-dimensional (3D) Zn-MOFs surface underwent aggregation. This

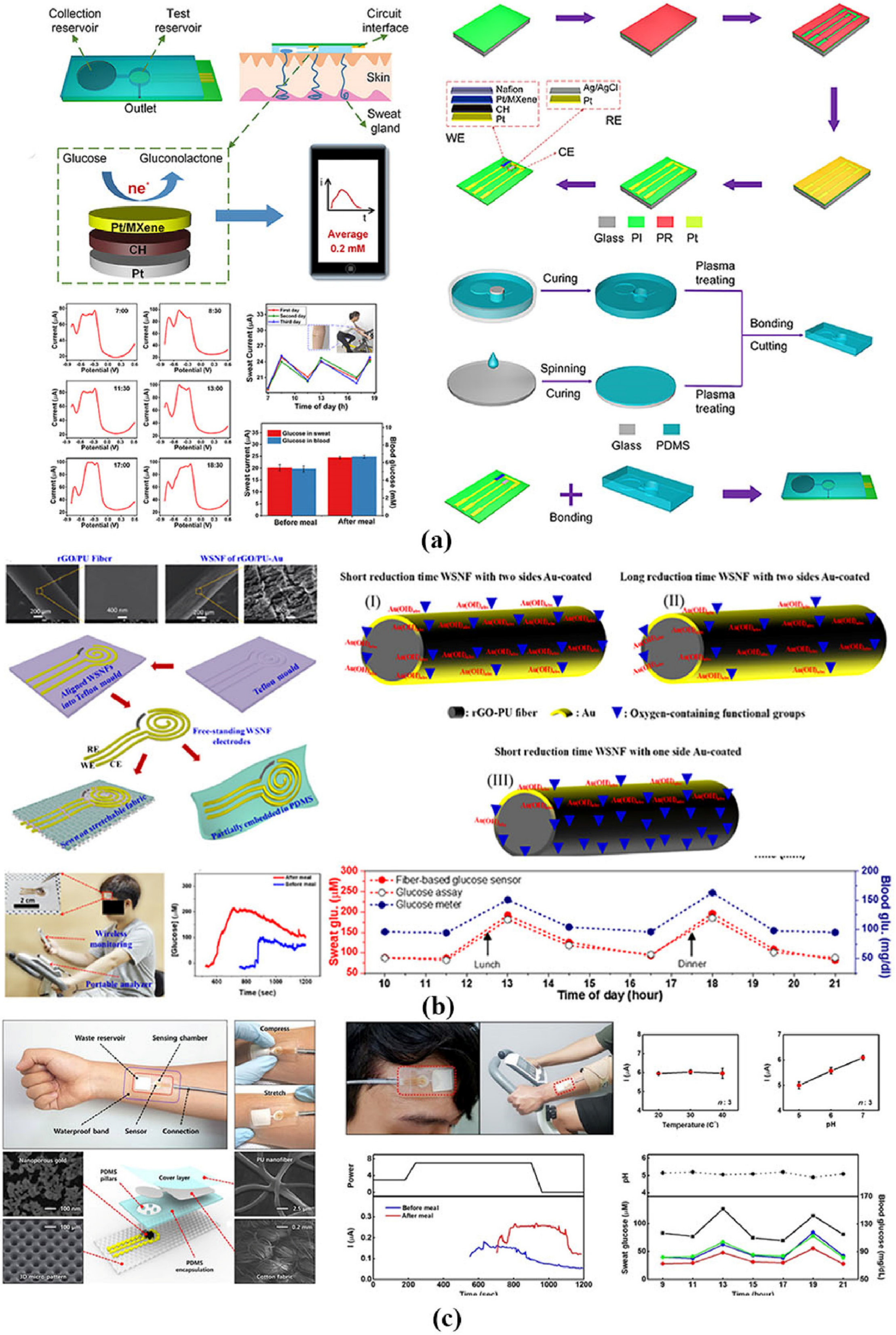


Fig. 11. (a) Conceptual scheme of the proposed flexible wearable non-enzymatic continuous glucose detection sensor on Pt/MXene. Replicated with permission from Ref. [174] from American Chemical Society. (b) Schematic of stretchable microfluidics-integrated biosensor patch. Replicated with permission from Ref. [180] from American Chemical Society. (c) Architecture and fundamental characteristics of the WSNF used as an electrochemical sweat glucose sensor. Replicated with permission from Ref. [181] from American Chemical Society.

was primarily caused by the fact that 3D Zn-MOFs had a larger surface energy than 2D Zn-MOFs, causing Ag crystals to aggregate and form substantial clusters on its surface. Therefore, the authors subsequently selected Ag/2D Zn -MOFs as the electrocatalyst$_2$ to detected H_2O_2 in active cells (normal and tumor cells) under the optimal conditions.

Although noble metallic nanozymes exhibit greater catalytic performance, they come at a comparatively expensive cost. It's a highly alluring idea to save material by optimizing preparation craft. Ju et al. [185]

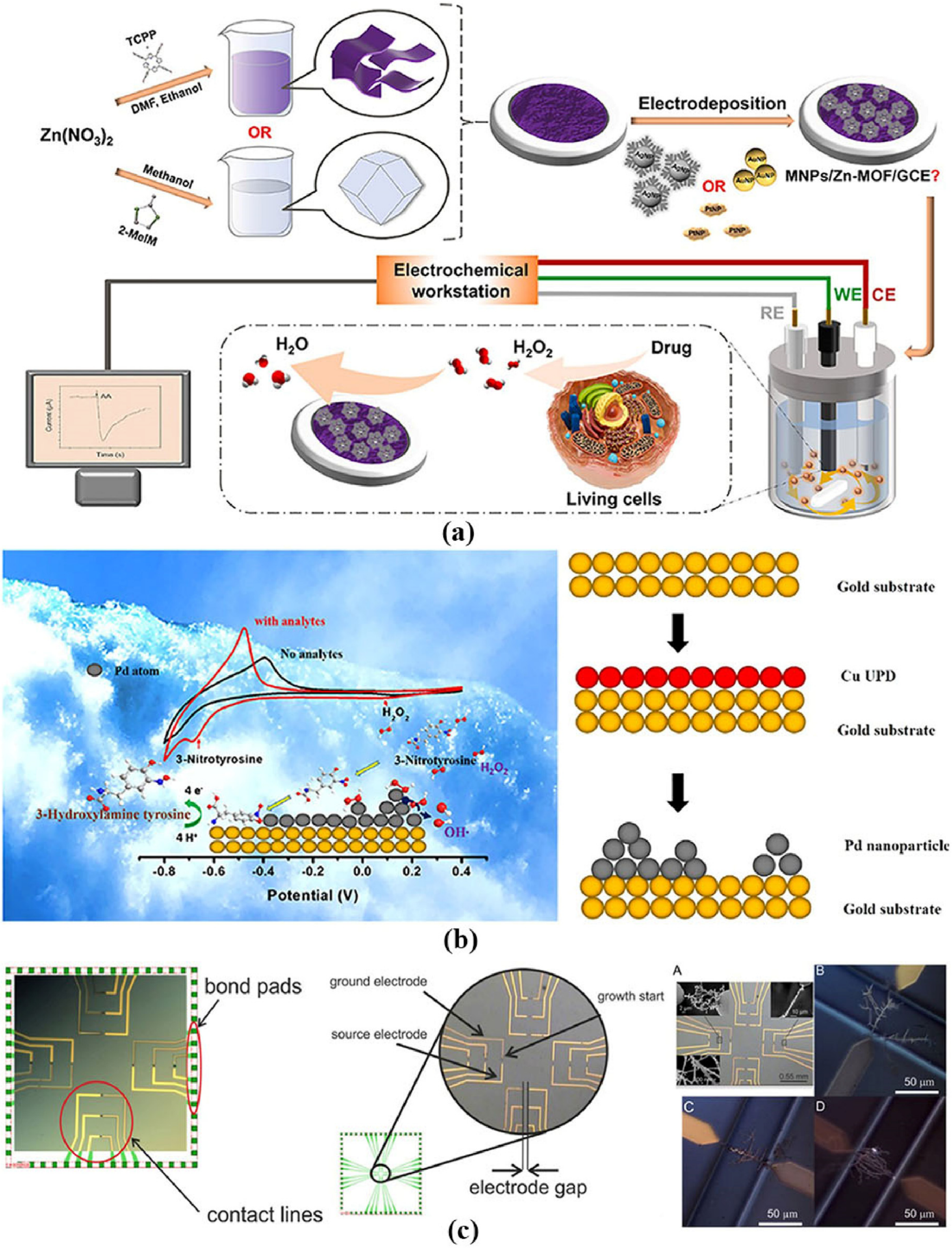


Fig. 12. (a) Schematic diagram of the major steps for fabricating MNPs/Zn-MOF modified electrodes and the H_2O_2 sensor used for in situ monitor of living cells released H_2O_2 from upon the stimulation of drug and transfer data to the electrochemical station. Replicated with permission from Ref. [184] from Elsevier. (b) Schematic representation of Pd/Au nano-catalyst electrode design and formation via copper UPD process. Replicated with permission from Ref. [185] from American Chemical Society. (c) Design of a single 13 × 13 mm chip and the optical microscopy image (A-D in the reference picture are the optical microscopy image of chip and Au (B), Pd (C), and Pd–Au (D) nanowire). Replicated with permission from Ref. [222] from Frontiers.

manufactured Pd/Au thin films on Au substrates by combining redox reduction processes with underpotential deposition (Fig. 12b). Pd in the precursor solution can undergo an in situ redox reaction with Cu pre-electrodeposited on the surface of the Au electrode. Ultrathin Pd atomic sub-monolayer films can be formed on the Au substrate electrode in this way. The design of Pd/Au film also reduced the amount of precious metals, which greatly reduced the synthesis cost. At the Au and Pd heterogeneous interface, an efficient electronic modulation caused changes in the lattice structure, which improved the electrocatalytic performance of the materials. The authors were successful in detecting H_2O_2 with high sensitivity and selectivity using Pd/Au films as probes. Furthermore, the no use of surfactants in this process efficiently prevented nanoparticle agglomeration and decreases electrocatalytic activity. By controlling the deposition potential and deposition time of the underpotential deposition, the coverage area of the atoms on the electrode surface can be regulated, and the thickness of the prepared metal catalytic layer can be precisely controlled. Nikolaev et al. [222] prepared Pd–Au nanowire electrodes by electrodeposition on a chip using a directed electrochemical nanowire assembly (DENA) method for H_2O_2 sensing applications (Fig. 12c). Metal nanowires and nano-dendrites can be directionally grown under high-frequency AC and DC bias voltages. By using this technique, metal nanowires that are electrodeposited on the device can be linked to external circuitry. The PdAu nano-dendrite electrodes assembled using the DENA method have diameters of 50 nm to several μm, which helps to reduce the amount of noble metals to lower the manufacturing cost. The preparation process avoided the conventional electrode surface modification step, which can effectively minimize the drift of the sensing response. The produced Pd–Au nanowire sensor exhibited sensing performance for H_2O_2 with a sensitivity of 18 $\mu A\ M^{-1}$.

Interestingly, the exceptional biocompatibility and the abundant enzyme-like catalytic activity of the metallic nanozymes allows flexibility in the design and development of flexible electrochemical POCT devices, enabling sensitive detection of different objects. Ko et al. [115] chemically immobilized Au@Pt bimetallic nanoparticles/graphene oxide (Au@PtNP/GO) on agarose microbeads surface (Fig. 13). The hybridized nanoparticles exhibit high peroxidase-like activity relying on the synergistic interaction between AuPtNP and GO, which can rapidly catalyze the oxidation process of TMB in the environment in the presence of H_2O_2. The use of Au@PtNP/GO nanozymes as a sensitive layer in electrochemical POCT device enables accurate detection of a wide range (from 1 μM to 3 mM) and low detection limit (1.62 μM) of H_2O_2. Moreover, the developed POCT device has a strong sensing performance in the detection of real samples of artificial urine.

5.1.3. *Uric acid and dopamine*

The byproduct of purine metabolism, uric acid (UA), serves as a significant antioxidant in the body [223]. In actuality, the body lacks the enzyme necessary to break down UA, and the intake and excretion levels are in a relative balance under normal circumstances. However, as people's diets changing, the increased intake of purines leads to more people with excessive UA and a series of diseases such as gout. This has drawn attention to the importance of uric acid analysis and detection. Wang et al. [37] reported an Au/Co bimetallic NPs modified hollow nanoporous carbon framework (Au/Co@HNCF) nanozyme material, constructing an electrochemical sensor to detect the trace UA in human serum (Fig. 14a). The synthesis process of nanozyme was broken down into two steps: ZIF-67 was first etched with Au(III) to create the core-shell structure, then pyrolyzed to create Au/Co@HNCF with a hollow structure. Considering both the high catalytic efficiency of Au/Co and the rich catalytic sites provided by the HNCF structure, the sensing platform has excellent sensing performance with a detection limit of 0.023 μM and a linear range of 0.1 μM to 2 500 μM. Additionally, the designed sensor assay results for detecting human serum samples were mostly in accordance with findings from Roche Diagnostics Cobas® 8000 analysis system, demonstrating a high level of accuracy.

Zhang et al. [192] constructed a sensor using Fe single-atom nanozymes (FeSAs) for the analysis and detection of uric acid content in resting sweat (Fig. 14b). Driven by electrostatic interactions, the amine group of UA launches an electrophilic attack on Fe–O. The electrons in the reaction system are redistributed and oxidation reaction occurs under the action of oxidation potential, generating an oxidative electrical signal at 0.3 V. The agarose hydrogel was used to collect and transport the sweat, which can efficiently collect resting sweat from the test area in a short period of time. The authors also created a pH sensor based on polyaniline for pH calibration to lessen the impact of pH variations on the electrochemical signal of UA. The sensing patch demonstrated excellent suitability in the analysis of resting and exercise sweat samples from volunteers.

Dopamine (DA) as a common interferer coexists with UA in physiological systems, of which oxidation potentials are similar [224]. It is surely quite challenging to accomplish extremely susceptible and discriminating electrochemical analysis for DA and UA. Xiong et al. [188] instead loaded MNPs onto the 2D covalent-organic frameworks (COFs)

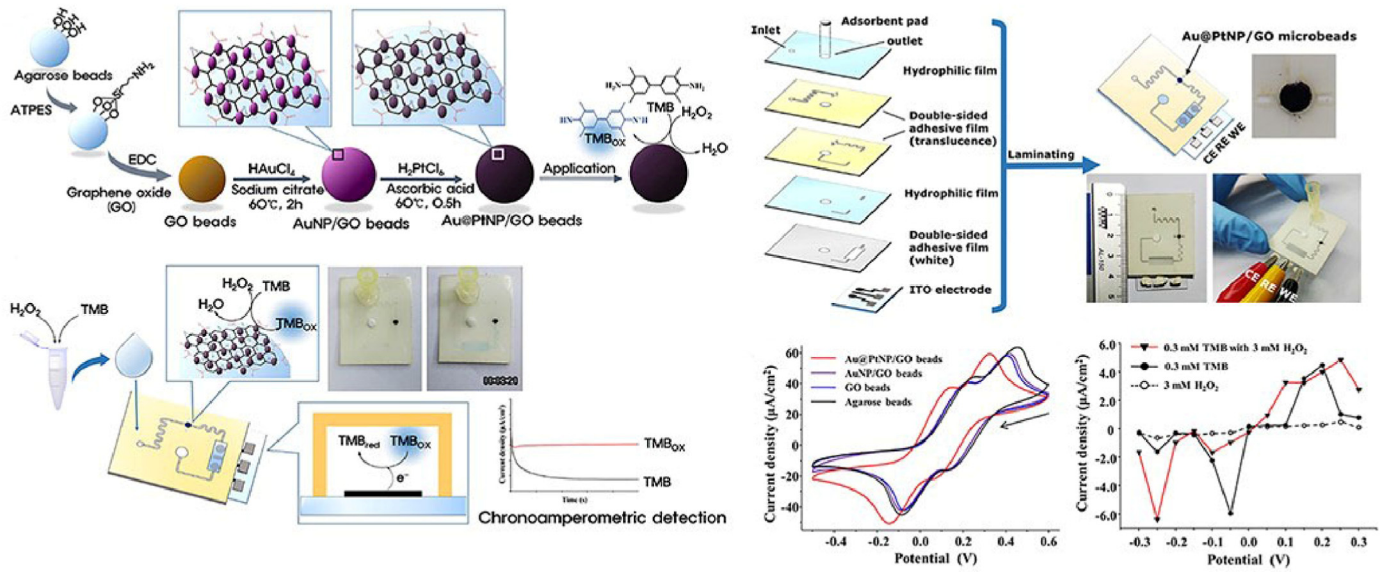


Fig. 13. Schematic diagram of the preparation of Au@PtNP/GO microbeads and H_2O_2 detection on electrochemical POCT devices with Au@PtNP/GO nanozymes. Replicated with permission from Ref. [115] from Elsevier.

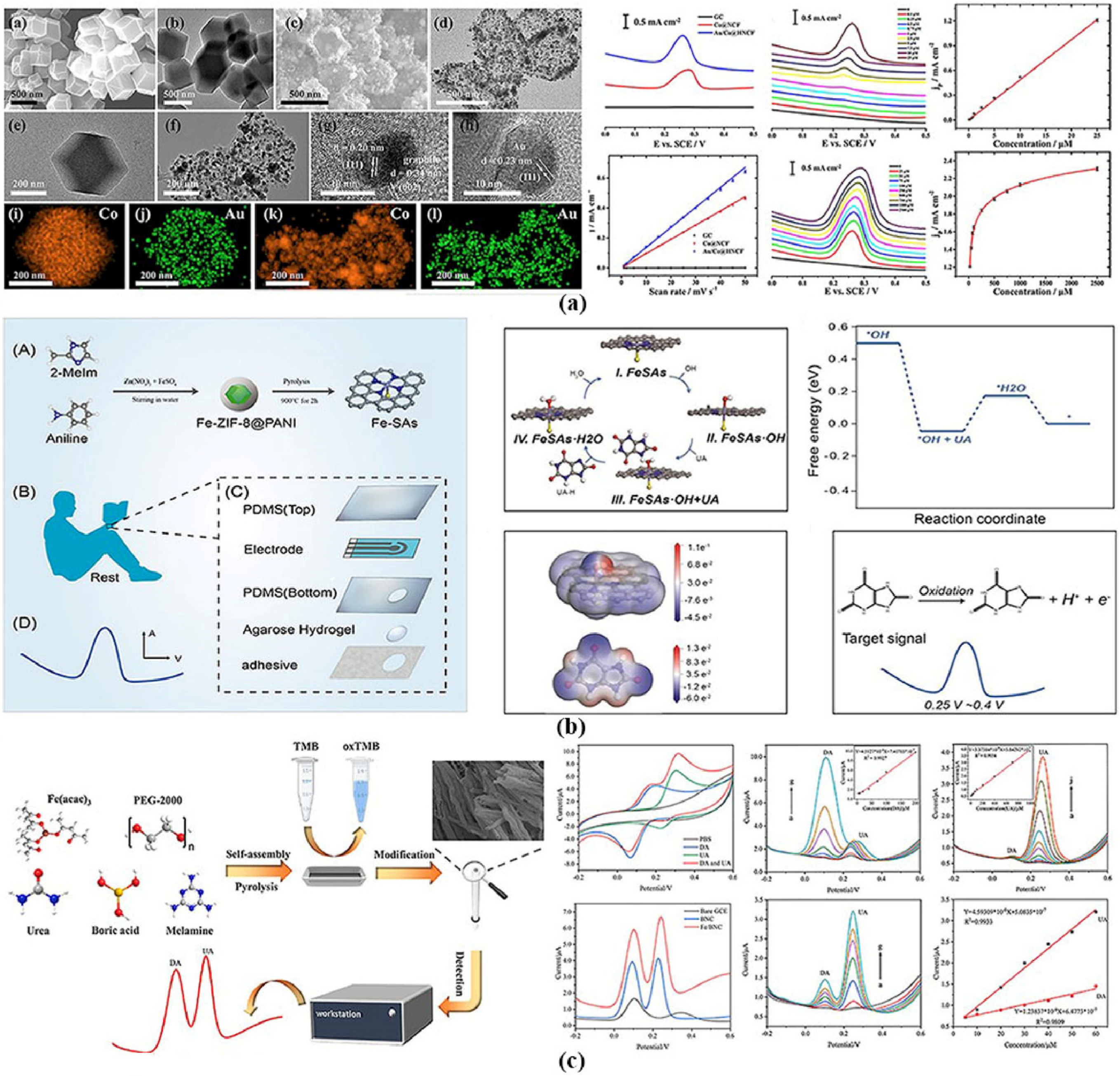


Fig. 14. (a) The Au/Co@HNCF-based electrochemical sensor to detect UA in the range of 0.1 μM to 25 μM and 25 μM to 2 500 μM (a-I in the reference picture are the morphology characterization of nanozymes). Replicated with permission from Ref. [37] from Elsevier. (b) FeSAs nanozyme-modified wearable hydrogel patch for precise analysis of uric acid at rest ((A)–(D) in the reference picture are the preparation process of nanozyme-based sensor). Replicated with permission from Ref. [192] from American Chemical Society. (c) Schematic representation of the preparation of Fe/BNC nanozymes biosensor for testing DA and UA. Replicated with permission from Ref. [191] from Elsevier.

and then further enhanced the electrocatalytic activity of material through calcination. The 2D COFs in the composites were transformed into carbon nanosheets (CN) during the carbonization process. The authors successfully detected DA and UA simultaneously using prepared CuNPs/CN, and the positions of their oxidation peaks were separated without non-interference. Notably, the CuNPs/CN based electrochemical sensor revealed a wide linear detection range with 0.015 μM to 140 μM for DA and 0.03 μM to 175 μM for UA.

Recently, Liao et al. [191] developed boron-nitrogen co-doped carbon nanotube-embedded Fe nanoparticle (Fe/BNC) nanomaterials for electrochemically determining UA and DA (Fig. 14c). The experimental results of differential pulse voltammetry (DPV) demonstrated that the Fe/BNC for simultaneous detection significantly separated the oxidation peaks of DA and UA, with the corresponding peak potentials being 104 mV and 348 mV. The excellent structural stability and oxidase-like activity of the Fe/BNC nanozymes dramatically increased the selectivity and sensitivity of determining UA and DA. This was since co-doping heteroatoms B and N into carbon nanotubes could provide additional active sites, modify the band gap and charge density and create numerous deficiencies, thus improving the electrocatalytic performance.

According to the above interesting findings, the unique physicochemical characteristics and catalytic activity of metallic nanozymes make them highly promising for use in the construction of POCT electrochemical sensors. Furthermore, the cost of fabricating devices has been remarkably decreased by the outstanding stability, reusability, and easy synthesis of metallic nanozymes. These properties favor the application of metallic nanozymes-based POCT electrochemical sensors in complex detection environments.

5.2. Metallic nanozymes as signal amplification tags of target analytes

5.2.1. Nucleic acid

For electrochemical detection of non-electroactive molecules such as nucleic acids, metallic nanozymes are typically utilized as signal tags to amplify the signal using their own redox catalytic activity or as nanocarriers of receptor molecules for signal amplification. When metallic nanozymes are used as carriers, the interaction with the target analyte often affects its enzyme-like activity, which in turn alters the corresponding electrochemical response.

Nucleic acid biomarkers can be used as a basis for the detection of cancer and neurodegenerative diseases. Accurate nucleic acid detection has a significant reference value and scientific relevance for clinical

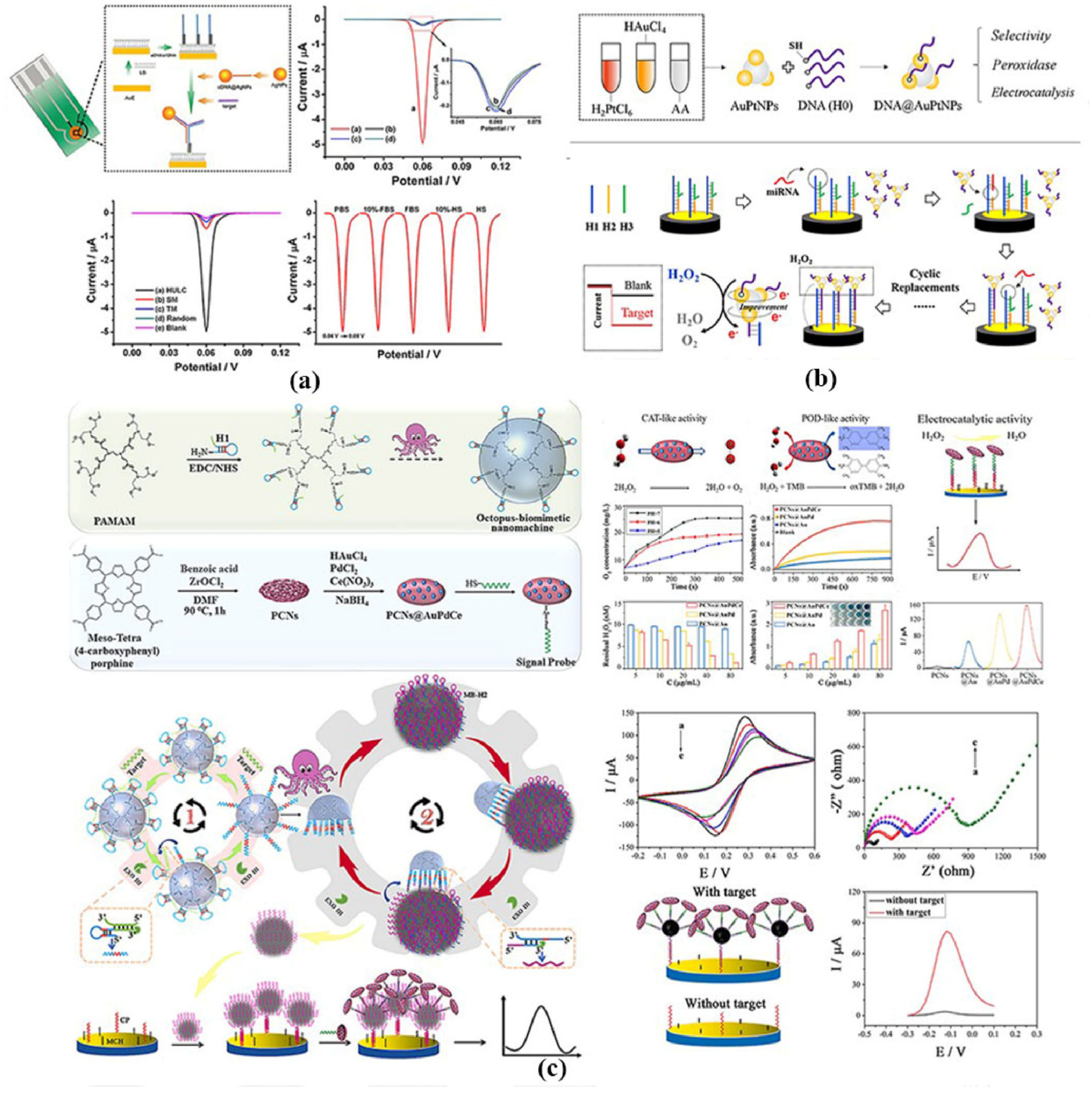


Fig. 15. (a) Schematic illustration of electrochemical detection of HULC based on antifouling LB coupled with AgNPs. Replicated with permission from Ref. [196] from Elsevier. (b) The principle of the electrochemical DNA sensor for the detection of miRNA-21. Replicated with permission from Ref. [195] from Springer. (c) The preparation process of PAMAM-H1 which looks like octopus. The synthesis process of PCNs@AuPdCe. The construction of electrochemical biosensors based on dual-core DNA nanomachines and PCNs@AuPdCe. Characterization for enzyme-like activities of PCNs@AuPdCe. Characterization of the electrode self-assembly process. Replicated with permission from Ref. [197] from Elsevier.

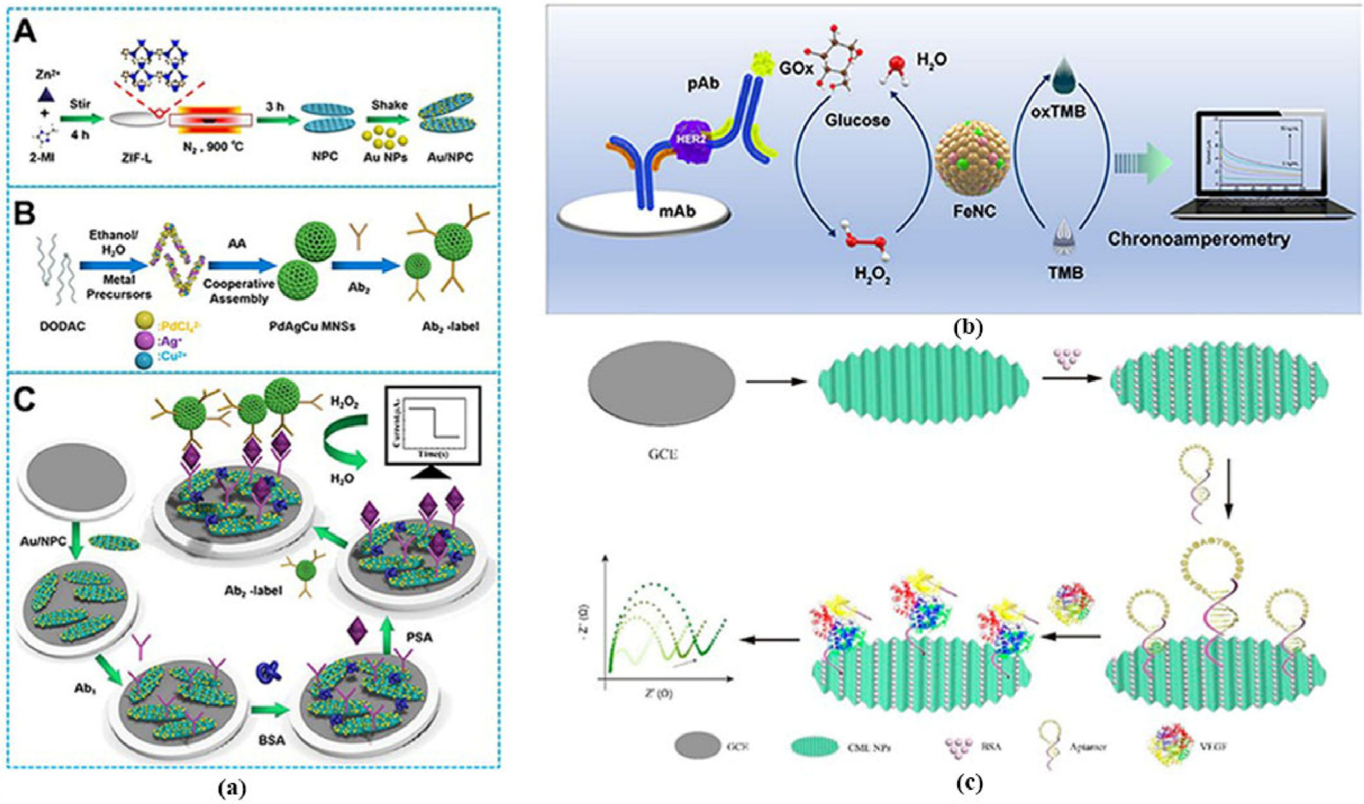
diagnosis and treatment of cancer and other disorders. Nucleic acid biomarkers mainly include DNA and RNA. Blood and other body fluids have extremely little nucleic acid marker concentration, which requires analytical tools with very high resolution to provide accurate quantitative detection results. Jiang et al. [196] realized sensitive and reliable electrochemical detection of highly upregulated in liver cancer (HULC), a long noncoding RNA, by combining lipid membranes with AgNPs (Fig. 15a). The immobilization of the ready cDNA@Ag on the electrode surface was guided by the target-induced y-shaped structure to provide an evident electrochemical signal. This revealed that using cDNA@Ag as a signal probe for the electrochemical detection of HULC is possible, which can greatly boost the sensor sensitivity. The issue of numerous non-target analytes in body fluids gathering non-specifically on the electrode surface was well-solved by the addition of lipid membranes. Signal noise reduction and false positive were also avoided. As a result, the sensor performed superbly in specificity control experiments.

Su et al. [195] synthesized AuPt bimetallic nanozymes combined with toehold-mediated DNA replacement effect for the electrochemical determination of miRNA-21 (Fig. 15b). The continuous loop chain substitution would be initiated once miRNA was identified by the toehold sequence. This leaded to the accumulation of AuPt NPs with peroxidase-like activity on the electrode surface, catalyzing the breakdown of H_2O_2 to produce an electrochemical response. Based on the strategy of signal amplification by metallic nanozymes, the sensor successfully determined miRNA-21 in serum with recoveries from 95.0 % to 102.4 %. Fuet al. [197] introduced exonuclease III (EXO III) and developed the dual core DNA nanomachines using target cell-free DNA (cfDNA) and octopus-shaped polyamine ssDNA (Fig. 15c). The electrochemical platform for the determination of cfDNA was constructed by integrating dual core DNA nanomachines with PCNs@AuPdCe hybrid nanozymes, in which PCNs@AuPdCe with various enzyme-mimicking activities was acted as signal tags. Owing to the signal amplification effect of PCNs@AuPdCe nanozymes and the amplification principle of DNA nanomachines, the sensing platform achieved the ultra-low quantitation of cfDNA with a detection limit of 84 aM.

5.2.2. Proteins

Proteins in human blood or body fluids, as an important class of biomarkers, are mainly derived from tissue metabolism and are products of gene expression. Protein biomarkers are typically kept at low levels in the body when genes are expressed normally. Once the level of gene expression is too high and the tissue is diseased, the level of certain protein biomarkers will be abnormal. Protein biomarkers can also be applied as an adjunctive indicator for illness early screening and therapy. Immunoassay, relying on the specific recognition regarding antibodies with antigens, is the most utilized method of protein detection [198,199,225–228]. Since the antigens and antibodies used in immunoassays are barely electrically active, most electrochemical immunosensors will label the antigen or antibody to initiate an electrochemical reaction. To improve the sensitivity of electrochemical immunoassays, researchers usually increase the loading of immune molecules on the electrode surface or enhance the electron transfer capacity of the electrode surface. The application of metallic nanozymes to electrochemical immunosensors not only loads a high content of tracer, but also catalyzes the substrate itself to play the role of signal amplification.

Shang et al. [199] developed a sandwich-structured electrochemical sensing platform using trimetallic PdAgCu mesoporous spheres (PdAgCu MNSs) hybrid nanozymes as a signal amplification label (Fig. 16a). The authors created nitrogen-doped porous carbon supported AuNPs (AuNPs/NPC) to modify on the electrode surface, which captured



(a) (b) (c)

Fig. 16. (a) Preparation process of Au/NPC, Ab2-label, and the sandwich-type immunosensor (A-C in the reference picture are the preparation process of nanozyme-based sensor). Replicated with permission from Ref. [199] from Springer. (b) Schematic illustration of a FeNC nanozyme-based electrochemical immunoassay via ELISA and chronoamperometry using the FeNC/H_2O_2/TMB nanozyme-based catalysis-decomposition oxidation system (HER2 human epidermal growth factor receptor. Replicated with permission from Ref. [198] from Springer. (c) Schematic illustration of VEGF aptasensor based on PdPtMo NPs. Replicated with permission from Ref. [205] from Frontiers.

primary antibody (Ab_1) and enhance the electron transport capacity. The secondary antibodies (Ab_2) were captured by the hybrid nanozymes PdAgCu MNSs on electrode surface, which then assembles them into sandwich structures. The PdAgCu MNSs can accelerate the breakdown of the probe H_2O_2, providing an obviously electrochemical response. Based on the above advantages, the sensing platform exhibited exceptional detection capability (linear range, 10 fg/mL to 100 ng/mL; detection limit, 3.29 fg/mL). Qiu et al. [198] prepared FeNC nanozymes with peroxidase-mimicking activity for the electrochemical immunoassay of human epidermal factor receptor 2 (HER2) (Fig. 16b). The FeNC nanozymes can catalyze the decomposition of H_2O_2 produced by HER2 through enzyme-linked immunosorbent assay (ELISA), resulting in the colorimetric oxidation of the substrate TMB. The authors realize the indirect quantitative analysis of HER2 by measuring the oxidation degree of the substrate TMB by the chronoamperometry. Mei et al. [205] created an electrochemical aptamer sensor based on PdPtMo NPs to identify vascular endothelial factor (VEGF) (Fig. 16c). Modifying PdPtMo NPs on the electrode surface not only served as a carrier for capturing DNA to connect the aptamer and the electrode, but also served as an electron exchange center to improve the detection sensitivity. When the target analyte is present, the hairpin structure of the captured DNA opened to bind to VEGF, resulting in an increase in impedance on the electrode surface. Based on the change in impedance before and after target binding, the authors investigated the sensing capability using electrochemical impedance spectroscopy, with a detection limit as low as 8.2 pg/mL.

5.2.3. Cancer cells

Tumor metastasis is the primary cause of cancer-related mortality. Circulating tumor cells (CTCs) known as cancer cells are those that circulate in peripheral blood after being spontaneously separated from cancer cells of primary or metastatic tumors [229]. Because tumor metastasis occurs primarily through the bloodstream, CTCs that have flowed into the vascular system or may be in the process of entering a metastatic site are detectable [230]. CTCs have important clinical relevance for tracking the development of tumors and comprehending the biology of disease. The low content of CTCs in the circulatory system and the heterogeneity of CTCs are important factors affecting their accurate detection. Since CTCs typically have overexpressed epithelial cell adhesion factors (EpCAMs) on their surfaces, the majority of published research work has identified CTCs by using anti-EpCAM antibodies to recognize the overexpressed EpCAMs on CTCs.

Yang et al. [206] developed an electrochemical sensing platform based on an aptamer consisting of Au@PdMo nanozymes and epithelium specific cell adhesion molecule (EpCAM) to identify circulating tumor cells (CTC) (breast cancer cells MCF-7 as the analytic model) (Fig. 17a). Effective dissociation and non-destructive release of CTC on the modified electrode can be accomplished in conjunction with electrochemical reduction and desorption. In this work, Au@PdMo acts as a signaling tag to amplify electrochemical signals by accumulating on the cell surface through interaction with MCF-7. The Au nanoparticles in Au@PdMo can provide a larger electrochemically active area to enhance the peroxidase-like catalytic activity of the nanozymes, which can help to further improve the detection sensitivity. Owing to the above features, the developed cell sensor possessed a detection limit as low as 2 cells/mL.

Li et al. [207] synthesized a trimetallic AuIrPt nanozymes with various enzyme activities and connected with EpCAM aptamers as signal amplification tags to build MCF-7 electrochemical sensors (Fig. 17b). The high electrocatalytic activity of AuIrPt towards H_2O_2 allowed its use as a signal amplification tag to significantly improve the sensing performance of the device. To guarantee that the cell sensing platform can reliably distinguish between target cells and other cancer cells, the authors employed a three-site recognition technique to introduce anti-MUC1 and anti-EGFR antibodies. Anti-MUC1 antibody acted as a capture probe1 (CP1) to capture and enrich target cells, and anti-EGFR modification on the electrode surface acted as CP2 to further improve the recognition accuracy. The sensor generated a response current only when the three antigens were simultaneously expressed on the cell surface, which greatly improved the specific recognition ability of the device.

5.2.4. Bacteria

Foodborne pathogens are pathogenic bacteria that can cause food poisoning or foodborne illnesses [231]. Numerous health issues, including renal disease, central nervous system abnormalities, and recurring intestine infections, can be brought on by foodborne bacteria. The development of rapid and sensitive universal methods remains a major challenge for the detection and identification of foodborne pathogens.

The Das group utilized the property of reversible control of the intrinsic enzyme-like activity of AuNPs nanozymes by the aptamer to

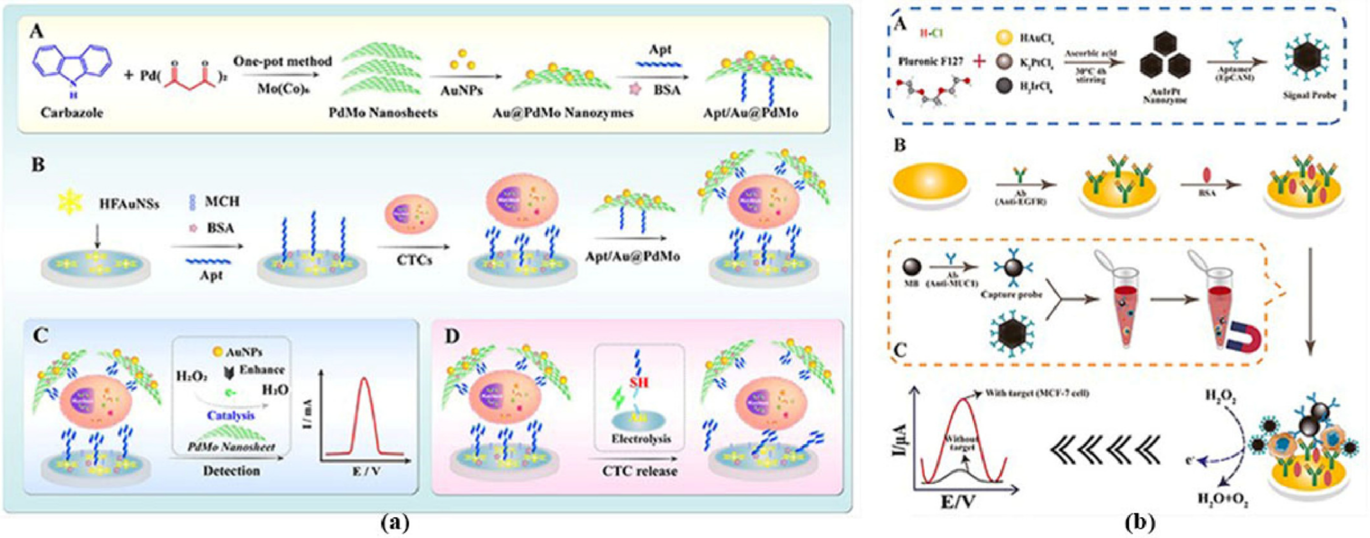


Fig. 17. (a) Preparation and mechanism of desorption of the cytosensor based on 2D Au@PdMo nanozymes and electrochemical reductive desorption for the detection and release of CTCs (A-D in the reference picture are the preparation process of nanozyme-based sensor). Replicated with permission from Ref. [206] from Springer. (b) Schematic representation of assembly procedures of the AuIrPt nanozymes-based electrochemical cytosensor for accurate determination of CTCs (MCF-7 cell as a model) (A-C in the reference picture are the preparation process of nanozyme-based sensor). Replicated with permission from Ref. [207] from Springer.

achieve targeted identification and detection of the bacterial pathogen Pseudomonas aeruginosa (PA) [209]. PA aptamer (F23) adsorbs on the surface of AuNPs by simple adsorption, covering the AuNPs catalytic activity site and inhibiting their mimetic peroxide function. Aptamer F23 is released from the surface of AuNPs based on its high affinity for PA when the target analyte is present in the detection environment. This allows the AuNPs to regain peroxidase-like activity and catalyze the oxidation of the substrate TMB, generating the corresponding electrochemical signal. This allows for the indirect determination of Pseudomonas aeruginosa. This indirect assay can rapidly detect PA within 10 min and has a detection limit as low as ~60 CFU/mL.

The eluted BIF layer specifically recognized Staphylococcus aureus in the environment and accurately captured the target analyte (Fig. 18) [210]. Au@Fc-Apt acts as a signaling probe and generates a current response proportional to the number of Staphylococcus aureus. This current response is mainly derived from the oxidation of Fc. The sensor prepared using this strategy can accurately detect target analytes down to 10 CFU/mL in complex milk matrices.

In the study of Li et al. [129], porphyrin metal organic framework PCN224 load with PtPd nanoparticles (PtPd@PCN224) as a signal label was used to constructed nanozymes-based electrochemical sensor for the determination of Burkholderia pseudomallei (Fig. 19). PtPd@PCN224 nanozymes with peroxidase-like catalytic activity can catalyze the reduction reaction of H_2O_2, which can act as a signal amplification tag to amplify the current signal. The Zr–*O*–P bond in PCN224 can interact with nucleic acid molecules to construct a specific recognition system. With the presence of the target analyte, the target-activated CRISPR/Cas14a carries out a *trans*-cutting activity program that can cut the phosphorylated ssDNA assembled on the electrode surface. This prevents the nanozymes from immobilizing the assembled on the electrode surface, resulting in a reduced catalytic reduction current response to H_2O_2. As the concentration of the target increased, the reduction current response progressively reduced. The strategy combining the strong electrocatalytic activity of the PtPd@PCN224 nanozymes with the recognition of CRISPR/Cas14a accomplished an extremely sensitive and selective assay for Burkholderia pseudomallei.

6. Conclusions and perspectives

As an alternative to natural enzymes, nanozymes have attracted the attention of many researchers due to their stability, simplicity of preparation, affordability, and scalability. Among the various nanozyme materials, metallic nanomaterials, which are typically thought of as physiologically inert, have been demonstrated to exhibit intrinsic enzyme-like activity because of their unique structure and properties. The superior physicochemical properties and catalytic activity of these metallic nanozymes make a hold the promise of replacing enzymes in electrochemical sensors for non-invasive or minimally invasive continuous medical monitoring. In this review, we discussed and analyzed the enzyme-like activity of metal nanozymes, the metal-based materials used for their preparation, the methods for adjusting the enzyme-like activity, and the advancements in electrochemical sensing research for biomarker detection. Despite a number of metallic nanozyme-based electrochemical sensors have been reported in the literature, the majority of commercialized devices still rely on natural enzymes. This is primarily because metallic nanozymes continue to face significant obstacles in practical applications due to their remaining shortcomings.

First, there is still a gap between the catalytic activity of metallic nanozymes and natural enzymes. This makes metallic nanozymes not yet completely replace natural enzymes for practical applications in multiple fields. Increasing the focus on the logical design of high-performance metallic nanozymes is necessary to attain catalytic activity similar to that of natural enzymes. The current mainstream research view is that the catalytic activity of metallic nanozymes is closely related to the electron transfer process on the surface of the material. There is a lack of discussion and analysis of the principles of metallic nanozymes for the detection of target analytes. Investigating the catalytic activity of metallic nanozymes has been carried out mainly through trial-and-error experiments. There is a lack of a sufficient number of research efforts centered on the theoretical investigations. It is necessary to combine experimental and theoretical studies to explain the catalytic reaction pathways for complementing the microscopic revelations. This will facilitate the design of nanostructures with high catalytic activity by providing a better understanding of the conformational interactions. In addition, the

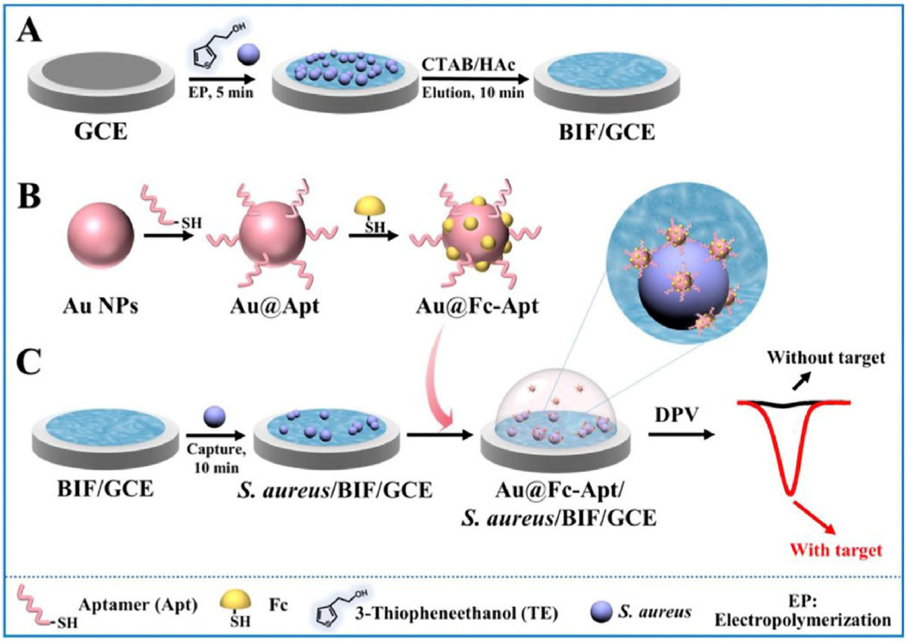


Fig. 18. Schematic illustration showing preparation process of the BIF-modified electrode and synthesis of the signal nanoprobe; fabrication of the dual synthetic receptor-based electrochemical sandwich sensor (A-C in the reference picture are the preparation process of nanozyme-based sensor). Replicated with permission from Ref. [210] from American Chemical Society.

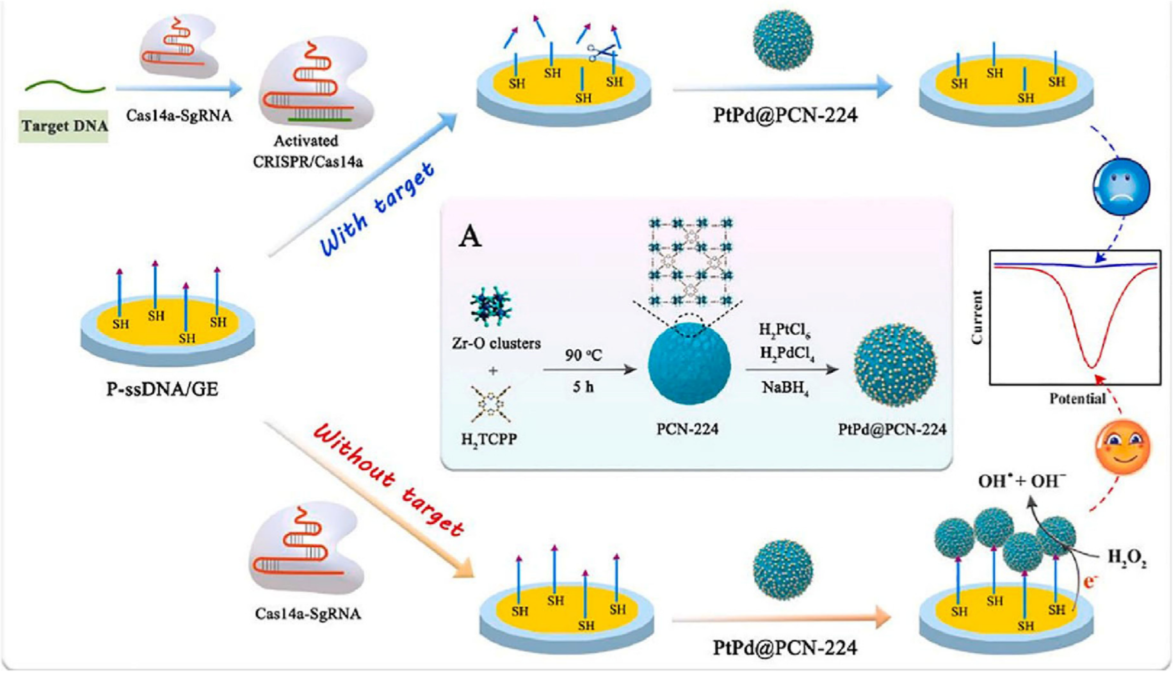


Fig. 19. Schematic illustration of CRISPR/Cas14a and PtPd@PCN-224 nanozyme-based highly sensitive electrochemical biosensor for B. pseudomallei DNA analysis (A in the reference picture are the preparation process of PtPd@PCN-224 nanozyme). Replicated with permission from Ref. [129] from Elsevier.

limited variety of enzyme-like activities of metallic nanozymes is one of the key factors restricting the scope of their catalytic applications. Currently published studies on metallic nanozymes in electrochemical sensing have focused on the catalysis of redox reactions. There is still a need to continue making efforts to fill the deficiency in hydrolase-like and isomerase-like activities of metallic nanozymes. Initially, it is possible to attempt more investigation by examining the materials utilized in the manufacturing of the metallic nanozymes. Noble and transition group metals, as well as associated alloy materials, continue to be the most commonly used substances for the generation of metallic nanozymes. Using carbon nanomaterials (e.g., graphene, Mxene) or porous materials (MOF) as frameworks to immobilize the metal active centers is promising for preparing multidimensional hybridized metallic nanozymes with changeable activities and increased catalytic efficiency. Reducing the metal active component to the single-atom scale is also a way to provide catalysts that maximize metal utilization.

Second, improving its particular selectivity is likewise one of the keys to implementing metallic nanozymes as a replacement to natural enzymes in the field of electrochemical sensing. The majority of metallic nanozymes usually reveal multiple enzymatic activities with limited ability to target catalytically to the substrate. Metallic nanozymes with multiple enzymatic activities at the same time may degrade the electroactive intermediates in reaction systems (e.g., H_2O_2 reduction reaction systems), which will lower the electrochemical response and affects the accuracy of the determination. Customizing the intrinsic enzyme-like activity of metallic nanozymes also need a thorough investigation of the mechanism underlying their tunable enzyme-like activity, modifying the ratio of their composition, or altering the reaction circumstances (such as pH). Surface modification with target-specific ligands (such as aptamers, nucleic acid molecules, antibodies, etc.) is another widely employed strategy to enhance the selectivity of metallic nanozymes. Although the specific ligands modified on the surface of metallic nanozymes can improve their targeted catalytic ability, this will inevitably cause some inhibition of their catalytic activity. This phenomenon can be used to guide the development of inhibition-type devices. Combining metallic nanozymes with molecular imprinting technology is another appealing alternative.

Third, the practical application of metal nanozymes in electrochemical sensing is just beginning. Diversifying the detection targets of metallic nanozyme-based electrochemical sensors is a key to ensure their usefulness, particularly in the field of health monitoring and medical diagnostics. Although metallic nanozymes show great potential in biomedical monitoring, their safety is a critical issue that must be considered. There is still a long way to go to develop low/non-toxic, high-performance metallic nanozymes, which will require a long period of validated optimization in clinical trials. In addition, obstacles like collection of test objects, calibrating benchmarks in complex environments, and contamination penetration must be also addressed. Developing technologies like multimodal integration and microfluidics has shown to be an effective way of overcoming these obstacles. The trend toward wearable intelligent sensing devices and mobile medical application terminals is becoming increasingly evident as artificial intelligence develops at a rapid pace. Choosing the appropriate flexible substrate compatible with different functional module integrated circuit boards is also essential. Currently, research on metallic nanozymes-based electrochemical sensing applications remains mainly at the laboratory stage. “Inconsistent activity in different batches" tend to occur during small-scale bottom-up chemical synthesis for the preparation of metallic nanozymes. The practical application of metallic nanozyme-based electrochemical sensors can only be possible through the successful resolution of these issues.

The above proposed problems and outlook about metallic nanozyme-based electrochemical sensors are mainly intended to provide researchers in the field with important information gathered by the authors so far. With advances in materials science, there are more material options available for the development of metallic nanozymes. This provided the possibility of metallic nanozymes to achieve more functionality. We are confident that the future of metallic nanozymes will not stop at mimicking the catalytic activity of natural enzymes. They are anticipated to be a better option than natural enzymes in the field of electrochemical sensing due to their special inherent features. With a deeper understanding of the catalytic mechanism of metallic nanozymes and the combination of multidisciplinary interactions, metallic nanozymes-based electrochemical sensing systems will show broader utility in the field of health monitoring.

Credit authorship contribution statement

Runan Tan: Conceptualization, Investigation, Writing- original draft, Writing - review & editing. **Panpan Jiang:** Conceptualization, Investigation. **Nan Gao:** Investigation. **Zhiwei Cai:** Investigation. **Yunbin He:** Conceptualization, Project administration. **Halina Grushevskaya:** Conceptualization, Project administration. **Gang Chang:** Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing - review & editing. **Yuxiang Wu:** Conceptualization, Funding acquisition, Project administration, Supervision. **Hanping He:** Conceptualization, Funding acquisition, Project administration, Supervision.

Declaration of competing interest

The authors declare no conflict of interest.

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