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Advanced sensing strategies for detecting zinc levels and zinc-related biomarkers in cancer pathogenesis

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ABSTRACT

Zinc and zinc-containing proteins are highlighted for their significant contributions to various physiological functions, with abnormal levels of these elements being associated with a wide range of diseases, including cancer, despite zinc itself not being considered a biomarker. Combining the detection of zinc and zinc-related biomarkers is an avenue to reliable and cost-effective monitoring. In this context, electrochemical sensing methods offer considerable advantages due to their rapid, simple, and cost-effective detection compared to standard methods. Recent advancements in electrochemical sensors have enhanced sensitivity for detecting low concentrations of zinc-related biomarkers present in early-stage cancer. Furthermore, incorporating carbon, gold, and bismuth nanostructures into sensor recognition elements enhances the capability for rapid, precise, and specific quantification of these biomarkers. This review discusses key zinc-related biomarkers, zinc levels and their roles in cancer development and progression, along with a comprehensive analysis of recent strategies to enhance the sensitivity and specificity of electrochemical sensors for zinc and zinc-related biomarkers.

1. Introduction

Zinc (Zn) is an abundant trace element in the body. The human body contains ~3 g of Zn, with muscles, bones, and liver/skin storing 60, 30, and 5% of its total, respectively [1]. It is involved in a variety of cellular processes, including cell proliferation, reproduction, immune function, and defense against free radicals. Zinc acts as a structural, catalytic, and co-catalytic component of various proteins, including enzymes and transcription factors. Over 300 enzymes require zinc for functionality and over 2000 transcription factors, involved in gene expression, need zinc for integrity and binding to DNA [2–6]. Zinc is found in two forms: as zinc ion and/or associated to a protein. Free intracellular/extracellular zinc is usually regulated by Zn-transporters (ZnT, ZIP-transporters, DCT-1), Zn-bindings (metallothioneins – MTs, p53), or Zn-sensing agents (MTF-1, ZnR/GPR39, AMPA, NMDA). It is important to mention that "free" zinc ion is predominantly weakly bound to the His-rich portion of ligands (Zn^{2+}/H^{+} exchanger) and rarely is zinc free in solution in healthy systems. While in protein-bound form, zinc presents structural (e.g. protein kinase C) or catalytic/co-catalytic functionality (e.g. Carbonic anhydrase, carboxypeptidase A, superoxide dismutase), being held by stronger binding forces coordinated by amino acids, with His being the most frequent, followed by Glu, Asp, and Cys [5,7–10].

Zinc-related biomarkers refer to measurable molecules or proteins whose expression or activity is influenced by zinc availability and homeostasis. They include zinc transporters (e.g., ZIP and ZnT families), zinc-dependent enzymes (e.g.,carbonic anhydrase [11] and matrix metalloproteinases), tumor suppressor p53, a protein regulating of the cell cycle [12] and transcription factors (e.g., zinc finger proteins [13]) and metallothioneins (MTs), proteins that bind heavy metals and protect cells from oxidative stress [14]. They play pivotal roles in cellular functions such as proliferation, apoptosis, and differentiation and are critical indicators of pathological states, including atherosclerosis, vascular diseases, neurodegeneration, immunologic disorders, the aging process, mutagenesis, and cancer [2,6,15,16]. These biomarkers have been the focus of research and development in disease mechanisms and their potential as diagnostic or therapeutic targets.

Several reviews have discussed the crucial roles of zinc in human health and disease. For example, Anzellotti et al. reviewed how, in the structure and function of proteins, zinc plays a critical role, in diseases [1]. In another review, Venturelli et al. demonstrated a positive correlation between zinc levels and the various forms of cancers and suggested that it could be used as a potential biomarker for cancers [17]. In

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a more specific review by Costello et al., the authors highlight how zinc, along with its transporters, plays an important role in pancreatic cancer, demonstrating the significance of zinc in various disease mechanisms [10]. Similarly, Lo et al. have combined several studies to demonstrate how the low concentration of zinc in prostate tissues can be indicative of cancer [18]. More recently, Sugimoto et al. have reviewed and summarized evidence that implicates low concentrations of zinc in serum and tissue as a common characteristic in various types of cancer [19]. Wang et al. also pointed out in their reviewing work a correlation between high zinc expression levels and cancer progression especially in breast cancer [8]. Other reviews focused on the development of sensors for detecting specific metalloproteinases [20–22], and the advancements in fluorescence sensors for zinc detection [23]. This work aims to examine the different strategies for detecting zinc-related biomarkers that are relevant to the diagnosis and prognosis of cancer, focusing on electrochemical approaches.

2. Zinc expression in cancer

Zinc-containing proteins play a crucial role in cancer initiation and progression, making them potential biomarkers for various cancer types [15,24]. Given their lack of specificity, zinc levels are not considered biomarkers but have been shown to correlate with disease progression, providing valuable insights into potential diagnostic or therapeutic targets. Studies report abnormal levels of "free" zinc and an alteration in the content of zinc-containing proteins in head and neck [25,26], breast [5,27–30], prostate [30–36], lung, pancreas [8,10,31,37], and other cancers. These advances have identified zinc and zinc-proteins as biomolecular targets for disease mediation [1,24]. Free zinc in cancer has received escalated attention, but its role is not yet fully established. Steady state levels are achieved through Zn-transporters/binding ligands that allow zinc uptake, distribution, and excretion [8,38]. In tumors, zinc homeostasis is unstable because of the abnormal transporter/binding ligand expression. This is directly correlated to tumor malignancy, contributing to the initiation and progression of cancer [4,5,7,8].

The SLC39 family of zinc transporters, known as ZIP, along with the SLC30 family, or ZnT, play critical roles in regulating cellular zinc homeostasis [39–41]. Imbalances in zinc homeostasis have been implicated in cancer initiation and progression [42]. Among them, ZIP7 (SLC39A7) and ZIP10 (SLC39A10) are members of the ZRT/IRT-like protein (ZIP) family, which regulate intracellular zinc levels by promoting zinc influx into the cytoplasm from the extracellular environment or intracellular stores. These transporters are crucial for maintaining zinc homeostasis, essential for enzymatic activity, transcriptional regulation, and signal transduction. Mutations in these genes disrupt zinc homeostasis, leading to cellular dysfunction and disease.

ZIP10 has been recognized as a key zinc transporter that affects the behavior of tumor cells. There is evidence that zinc and ZIP10 contribute to the migratory activity of metastatic breast cancer cells, suggesting that ZIP10 may be a putative marker for the metastatic phenotype in breast cancer [27]. There is also emerging evidence that ZIP10 is a functional oncogene in gastric cancer [43]. Data indicate that targeting CK2, a downstream effector of ZIP10 activity, could serve as an alternative therapeutic strategy for gastric cancer patients with high ZIP10 expression [43]. These findings further underline the importance of ZIP10 not only as a biomarker but also as a potential therapeutic target. ZIP7 is localized to the endoplasmic reticulum (ER) membrane and is hypothesized to be responsible for mobilizing zinc from the ER, a zinc storage site, into the cytosol. This zinc signaling is vital for regulating growth factor signaling pathways, such as PI3K/AKT and MAPK/ERK. Mutations in the ZIP7 gene can result in severely decreased levels of cytosolic zinc, impaired cell proliferation, and activation of ER stress. In breast cancer cells, ZIP7 activation stimulates key signaling pathways like MAPK, PI3K, and mTOR, driving cell growth and proliferation [44]. It is notably upregulated in gastric tumor models [45] and plays a vital role in epithelial cell self-renewal [46]. ZIP7 is also essential for colorectal cancer (CRC) cell survival and growth, contributing to tumor development. Suppression of ZIP7 significantly impairs colon cancer cell viability and disrupts cell cycle progression, inducing G2/M arrest and triggering early and late apoptosis. This knockdown enhances PARP cleavage, upregulates pro-apoptotic proteins like Bad and Caspase-3, and downregulates the anti-apoptotic protein Bcl-2 [47].

Abnormal levels of zinc have been reported in tissues, fluids, and other secretions of cancer patients. Zinc concentration in cancerous prostate tissue is ~75% lower than in normal prostate and significant changes in serum, urine, and saliva zinc levels have been observed in prostate cancer patients [4,8,31–34]. The opposite observation has been found for breast cancer patients, where there is an increase of ~70% of zinc level in cancerous tissue when compared to healthy tissues, followed by abnormally low levels of serum, salivary and urinary zinc [5,7,8]. Table 1 summarizes the zinc expression in different types of cancer.

Zinc affects cancer growth, but measuring its levels is inconsistent because 1) Factors such as the cancer microenvironment, diet, and individual biology influence zinc levels [7,8] and 2) Standard measurement techniques, like atomic absorption spectrometry or inductively coupled plasma mass spectrometry, often yield inaccurate results due to the low concentration of free zinc in body fluids (e.g., blood plasma contains about 1 μg/ml) [15,16]. More standardized studies are needed to clarify zinc's role in cancer.

3. Zinc-metalloprotein expression in cancer

3.1. Carbonic anhydrase (CA)

Cancer cells obtain energy through aerobic respiration of glucose or

Table 1
Abnormal zinc levels in tissues, fluids, and secretions of cancer patients.

Type of cancer	Zinc expression	Zn-transporter/cause associated	Ref.
Prostate	Reduction of the zinc level in tissue and serum (~80%). Increase excretory zinc in urine (from 115 to 977 ng ml^{-1} to 117–1859 ng ml^{-1}) and saliva.	Lower expression of ZIP1	[30–36,48]
Breast	Increase the zinc level in tissue (from 7.2 to 8.6 μg/g to 10.3–23.5 μg/g). Reduction of zinc level in serum (from 97.75 to 126 μg/dl to 87–104 μg/dl).	Overexpression of ZIP6 (LIV-1), ZIP7, ZIP9, ZNF468 and ZIP10.	[5,27–30,49–52]
Oral	Increase of the zinc level in serum (from 64.57 ± 31.54 mg/dl to 113.51 ± 52.30 mg/dl) and saliva (from ~175 ppb to ~411 ppb)	Associated with the inflammatory process of lesions where zinc participates actively in transcription and the enzymatic antioxidant processes.	[25,26,53]
Lung	Lower level of zinc in serum when compared to the health group (from 1.14 ± 0.27 mg/L to 0.028 ± 0.007 mg/L)	Decreased zinc may be because of deformed protein structures (thymidylate synthetase, dihydrofolate reductase, p53, p16, K-ras)	[54,55]
Pancreas	Increase of zinc levels in the tissue	Overexpression of ZIP4 and ZIP3	[8,10,31,37]
Liver	Decrease of intracellular zinc levels. Decrease of zinc levels in tissue (~55–75%).	Downregulation of ZIP14	[56,57–60]

anaerobic glycolysis, both producing metabolic acids (CO2, lactate–, and H+). To maintain intracellular pH, these acids are extruded to the extracellular environment. CO2 is passively diffused through the plasma membrane, while lactate is removed via monocarboxylate transporters [61–64]. However, this acid removal is insufficient for efficient pH regulation, necessitating additional pH regulatory proteins such as NHE1, ATPases, NBCs, and carbonic anhydrase (CA) [63,64]. CA is an extracellular zinc metalloenzyme that catalyzes the reversible hydration of CO2 to bicarbonate and protons ($CO2 + H2O \leftrightarrow HCO3 + H+$) [61,62]. As discovered by Keilin and Mann in 1941 [65], CA expression is low in normal tissues but elevated in hypoxic tumors like the brain, breast, lung, and others [61]. Of its 12 human isoforms, CAI, CAII (cytoplasmic), CAIX, and CAXII (membrane-associated) are linked to cancer progression [63,64]. CAIX is the most studied, present in 85% of hypoxic tumors [61–64], However, CAI and II are emerging biomarkers for colorectal, lung, and hematological cancers [66]. CA's role in regulating intracellular pH contributes to an acidic extracellular environment, promoting tumor cell invasiveness and growth [62,63].

3.2. Matrix metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) are the second most studied metalloproteins in biomedical research due to their role in numerous diseases [65]. MMPs are zinc-dependent extracellular endopeptidases responsible for degrading extracellular matrix (ECM) proteins such as collagen, laminin, elastin, and fibronectin [67–69]. The 24 human MMPs are categorized by ECM specificity and structure (secreted or membrane-anchored), including collagenases, gelatinases, stromelysins, matrilysins, and membrane types [68,70]. MMPs generally consist of three domains: pro-peptide, catalytic, and hemopexin. The pro-peptide domain activates the enzyme, the catalytic domain (containing two zinc ions) drives proteolysis, and the hemopexin domain binds substrates like collagen [67,69]. All MMPs, except MMP-7, −26, and − 23, have the hemopexin domain [67]. MMP activity is influenced by both pH and temperature, making their thermosensitivity a critical factor in applications involving their detection or assessment of proteolytic performance. In general, MMPs exhibit a specific temperature range within which they remain stable and active. For instance, MT1-MMP is active between 10 °C and 55 °C [71]. However, within this range, temperature variations can significantly impact enzymatic activity. Elevated temperatures up to 37 °C enhance the activity of secreted MMPs such as MMP-9 and MMP-2, while lowering the temperature to 33 °C reduces their activity [72]. Furthermore, in vivo studies indicate that physiological temperatures promote higher MMP-9 activity [73]. This underscores the importance of carefully regulating temperature in experimental and clinical settings, as it directly influences the enzymatic activity, stability, and overall effectiveness of MMPs in biological processes and detection systems [72]. For sensing applications, maintaining optimal temperature conditions is essential for reliable results. Fluctuations outside the ideal range may either inhibit MMP activity or denature the enzyme, leading to inaccurate detection. Temperature control mechanisms, such as thermoregulated sensors or devices, should be implemented to ensure enzymatic stability. Additionally, understanding the temperature dependence of specific MMPs enables the fine-tuning of detection systems, improving both sensitivity and specificity. By considering these factors, researchers can enhance the design and performance of MMP-based sensing technologies, ensuring their robustness and utility in diverse biological and diagnostic applications.

MMPs regulate cell behaviours such as proliferation, adhesion, migration, differentiation, and apoptosis [69,70,74]. Normally expressed at low levels, dysregulation and overexpression of MMPs are linked to diseases including neurodegenerative disorders, cardiovascular issues, arthritis, CNS disorders, and cancer [67,68,70]. Overexpression of MMPs is especially associated with cancer progression, metastasis, and aggressiveness [75]. MMPs significantly alter the tumor microenvironment, and their expression is notably different in cancerous versus healthy tissues 43,44,46,47. MMP-2, −7, −9, −11, and − 14 are frequently overexpressed in various cancers [74,76]. MMPs contribute to cancer by influencing growth signals, affecting TGF-Beta and EGFR (MMP-2, −9, −14), modulating apoptosis (MMP-7), and promoting vascularization through VEGF regulation [69]. Extensive reviews of MMP function in cancer are available [69,70,74], with tissue MMPs serving as potential biomarkers, although their quantification remains complex (Table 2).

3.3. Tumor suppressor p53

p53 is an intracellular nuclear transcription protein associated with over 50% of human cancers due to loss-of-function mutations in the p53 gene [123–125]. It has three domains: transactivation, DNA-binding, and oligomerization. Most mutations are in the DNA-binding domain, which impairs its function [126,127]. p53 relies on zinc to stabilize its DNA recognition motifs but becomes unstable without zinc at body temperature [124]. p53 is crucial for DNA repair and inhibiting abnormal cell growth, and its loss leads to uncontrolled proliferation [123,128]. Mutant p53, found in over 3000 cancer mutations, accelerates cancer progression and can appear at any stage [124,126,129]. It interacts with oncogenic genes like MDR1, c-myc, and EGFR, contributing to aggressive cancers [123–125]. p53 mutations are common in solid tumors compared to hematological malignancies, with high prevalence in difficult-to-treat cancers like lung, breast, ovarian, and head & neck cancers (Table 3) [127,130]. Detecting mutant p53 helps in understanding cancer aggressiveness and guiding treatment, but developing strategies to target specific mutants remains challenging and requires further insight into p53's structure and behavior.

3.4. Zinc finger proteins (ZNFs)

Zinc finger proteins (ZNFs) are characterized by cysteine (Cys) and histidine (His) residues, stabilized by a zinc ion [131–133]. About 3% of human genes encode C2H2 proteins, making them one of the most prevalent protein motifs and crucial genomic regulators [134]. Despite their abundance, the specific roles of ZNFs are not fully understood. They are implicated in essential biological processes such as apoptosis, cell differentiation, proliferation, and chromosomal organization [1,132,135], and are key to tissue development [131,132]. Abnormal ZNF expression contributes to cancer progression at various stages, from carcinogenesis to metastasis. ZNFs, due to their role as transcription factors, can function as either oncogenes or tumor suppressors [133]. Emerging evidence also shows that ZNFs act as structural proteins regulating cancer cell migration and invasion [132,133,135]. Understanding ZNFs in the cancer environment could provide insights into one of the largest protein superfamilies in the human genome.

ZNFs exist in different conformations, such as CysCys (CC) or Cys-His (CH) motifs, including C2H2, C2HC, and C2C2 types [1,132,135,136]. The C2H2 group is the largest and most classical, with around 6000 members [131,137,138]. Within this group, ZEB1, ZNF750, ZNF281, and ZNF148 are known to be involved in cancer progression [132]. ZEB1 is oncogenic, promoting tumor invasion and metastasis, and its abnormal expression is found in pancreatic, lung, liver, osteosarcoma, breast, and colon cancers [132,139]. ZNF281 is an oncoprotein linked to DNA damage and epithelial-mesenchymal transition, with abnormal expression in colorectal cancer [132,140]. ZNF750 is abnormally expressed in esophageal, lung, and cervical tumors [132], while ZNF148 stabilizes p53 and influences cancer growth and apoptosis, with elevated expression in breast, melanoma, and gastric cancers [132,141,115].

3.5. Metallothioneins (MTs)

Metallothioneins (MTs) are cysteine-rich proteins that bind metals [38,142,143], and some authors classify them as a type of zinc finger protein [131,137]. While zinc is their primary binding partner, MTs also

Table 2
Abnormal expression of most relevant MMPs in cancer.

MMPs	Mechanism	Cancer	Serum expression ($ng.ml^{-1}$)		Tissue expression ($ng.mg^{-1}$)		Ref.
			Healthy	Unhealthy	Healthy	Unhealthy	
MMP-2	Proteolytic degradation of extracellular proteins in tumor invasion, collagenolytic pathway driver for lymphatic vessel formation, tumor angiogenesis [74,76]	Breast	~594	~695	~6.7	~30.5	[77–79]
		Ovarian	~227	~280	~470	~1200	[80,81]
		Prostate	~471	~893	~2	~8.8	[82–84]
		Head & Neck	ns	ns	~3.8	~10.2	[70,85,86]
		Lung	~700	~900	~8	~12	[87,88]
MMP-7	Contributes to invasive potential, proliferation, anti-apoptotic, immune surveillance [74,76]	Ovarian	~3	~11	~1	~4	[80,89]
		Colon	~4	~13.5	~0	~2.5	[70,90,91]
		Brain	~1.5	~2.5	-	-	[92]
		Renal	~2.9	~6.6	*	*	[93,94]
		Head & Neck	ns	ns	-	-	[95]
		Lung	~2	~4	*	*	[96,97]
MMP-9	Proteolytic degradation of extracellular proteins during tumor invasion [74,76]	Breast	~270	~371	~2	~12	[78,98]
		Bladder	~417	~786	*	*	[99–101]
		Prostate	~169	~486	*	*	[83,102]
		Head & Neck	~291	~1590	~4	~11	[70,85,103]
		Lung	~436	~1390	~31	~63	[88,104]
MMP-11	Produced by peritumoral stromal fibroblasts; regulates early tumor invasion, implantation, and expansion; prevents apoptosis of early cancer cells [74,76]	Breast	~8	~54	~0.2	~0.6	[105,106]
		Colon	~6	~39	*	*	[107,108]
		Gastric	~6.5	~42	*	*	[109,110]
		Head & Neck	~5	~17	*	*	[111,112]
		Lung	~2.5	~8	~0.01	~0.05	[113,114]
MMP-14 (MT1-MMP)	Cleaves other MMPs (mainly MMP2) to activate them, role in invasive blood vessel growth, and promote metastasis. In vitro has been shown to promote invasion [74,76]	Breast	~8.5	~17	*	*	[115,116]
		Ovarian	~6	~12	*	*	[117,118]
		Gastric	~8	~39	~1.3	~3.6	[119,120]
		Head & Neck	-	-	*	*	[121]
		Lung	-	-	*	*	[122]

"ns" – no significant difference; "*"MMP is overexpressed in cancerous tissue, but quantification (to $ng.ml^{-1}$) was not obtained; "-"data not available.
Some values were converted to ng. ml^{-1} from relative expression.

Table 3
Percentages of samples with mutated p53 by tumor type.

Type of cancer	Ovarian	Lung squamous cell carcinoma	Head & Neck	Colon and Rectal	Lung adenocarcinoma	Bladder	Breast	Glioblastoma	Uterine	Leukaemia	Renal
(%)	94.6	79.3	69.8	58.6	51.8	50	32.9	28.3	27.8	7.5	2.2

Adapted from [129].

bind other metals, including lead, copper, cadmium, mercury, platinum, and silver, with high affinity [144]. There are four main isoforms of MT (MT1, 2, 3, and 4), with MT1 and MT2 being the most prevalent in humans [38,143,144]. MTs play key roles in metal regulation, such as controlling zinc absorption from the intestine, maintaining zinc serum levels, storing and sequestering metal ions, donating metals to enzymes, interacting with zinc-based transcription factors, and regulating zinc and copper homeostasis [38,144]. Additionally, they protect against metal toxicity and oxidative damage [27]. Due to their diverse roles, MTs are implicated in various diseases, including neurodegeneration, cardiovascular and metabolic disorders, and cancer [144]. In cancer, MTs are involved in development, treatment resistance, and prognosis [142,143]. Tumor cells utilize MTs for transport, apoptosis inhibition, proliferation, immunomodulation, and enzyme activation [38]. Krizkova et al. have summarized the expression and regulation of MT isoforms in different cancers. MTs can serve as prognostic markers due to their abnormal expression in tumors. However, this expression varies—MTs are upregulated in some cancers and downregulated in others [143]. For instance, in prostate cancer, healthy tissues show significant MT staining, while malignant tissues exhibit a 73% reduction in MT immunostaining intensity [145]. Conversely, in head and neck cancer, 84% of cancerous tissues show higher MT expression compared to healthy tissues [146,147]. Most studies use immunohistochemical assays to assess MT expression in tumors [38], but abnormal MT levels have also been detected in serum samples. For example, testicular cancer patients show higher MT levels (~0.6 $mg.ml^{-1}$) compared to healthy individuals (~0.4 $mg.ml^{-1}$) [148], and MT expression in liver cancer is significantly lower (~0.5 μM) compared to healthy individuals (~1 μM) [149].

4. Detection of metals and metal-containing proteins in cancerous samples

Early cancer detection is crucial for controlling disease progression. Despite advances in diagnostic methods like ultrasound, MRI, and biopsy, they lack the necessary accuracy for early-stage detection [150–153]. Often, by the time cancer is diagnosed, cancerous cells have already spread significantly [152]. Biomarker detection offers a reliable and cost-effective strategy for early detection. Zinc and zinc-containing proteins are of particular interest in oncology as key biomarkers due to their role in cancer.

The analysis of trace elements such as zinc, iron, and cobalt in biological fluids and tissues is typically performed using atomic absorption and mass spectrometry techniques. These include flame atomic absorption spectrometry (FAAS), graphite furnace atomic absorption spectrometry (GFAAS), inductively coupled plasma atomic emission

spectrometry (ICP-AES), and inductively coupled plasma mass spectrometry (ICP-MS) [154,155]. While these methods are sensitive and accurate, their complexity, high cost, and challenging sample collection limit their widespread use in clinical settings [154–156]. FAAS is the most commonly used technique due to its lower cost, but its sensitivity is often insufficient for many biological samples [156].

Protein detection and quantification often rely on methods like PCR, immunoassays, southern blotting, DNA sequencing, and FISH [153,157]. ELISA is the most widely used platform for protein detection [152,153,157], relying on colorimetric or fluorescent signals to visualize protein binding 126. However, ELISA is time-consuming, costly, and may lack the sensitivity required to detect low protein levels in early cancer stages, leading to false negatives [151,153]. Recently, LC-MS, combining liquid chromatography with mass spectrometry, has become a leading technique for cancer biomarker detection due to its high sensitivity and resolution [150,152,158]. Despite its benefits, LC-MS is expensive and requires complex sample preparation, limiting its routine use [157,158]. Thus, developing alternative cancer biomarker detection methods, including for zinc-containing proteins, is of great clinical interest [151,153,159]. Electrochemical techniques have shown promise for cancer biomarker detection due to their high sensitivity, specificity, simplicity, and potential for miniaturization, making them ideal for clinical and point-of-care applications [160,161].

5. Electrochemical detection

Since its first development, in 1950s, electrochemical sensors have been widely applied for environmental monitoring [162–164] to the clinical field, including diabetes [165], cardiac diseases [166], bacterial infection [167], neural disorders [168] and cancer [160,161]. Great progress in the development of electrochemical sensors has been achieved with the incorporation of nanotechnology [164]. By enhancing selectivity, sensitivity, and limit of detection; new materials, applications, methodologies, and strategies are currently applied to monitor key biomarkers for research, treatment directions, therapeutic effectiveness, and as an additional diagnostic tool [169].

5.1. Strategies to increase the specificity and sensitivity of electrochemical sensors

Challenges in electrochemical detection include real-time and in situ measurement of biomarkers for early disease detection [170]. A non-invasive approach is increasingly emphasized, focusing on monitoring sweat, saliva, and urine biomarkers. Key concerns here are sensitivity and specificity [170]. Sensitivity refers to the sensor's ability to respond to changes in analyte concentration, directly related to the limit of detection (LOD), which is the lowest measurable concentration of the target species [170,171]. On the other hand, specificity, or selectivity, is determined by the unique binding affinity between the designed electrode and a particular species in the analyte [170]. Low sensitivity and specificity often result from interference by substances absorbed on the electrode surface, affecting signal measurement [171,172].

To address this, strategies have been developed to modify the electrode surface and minimize interference (Fig. 1). Common approaches include incorporating nanostructures and immobilizing recognition elements on the electrode surface [170–172]. Nanomaterials, such as carbon-based structures and metals, are frequently used to modify electrode surfaces. Their high surface area and electrical conductivity enhance the active surface area, significantly boosting sensitivity [171–173]. Moreover, nanostructures provide a biocompatible environment for biomolecules, allowing a greater number of biomolecules to be immobilized on the electrode surface [174]. While nanomaterials improve sensitivity, the use of recognition elements that bind specifically to the target species enhances selectivity. Selective molecules, such as enzymes and antibodies, facilitate specific interactions and help reduce false positives [172,173].

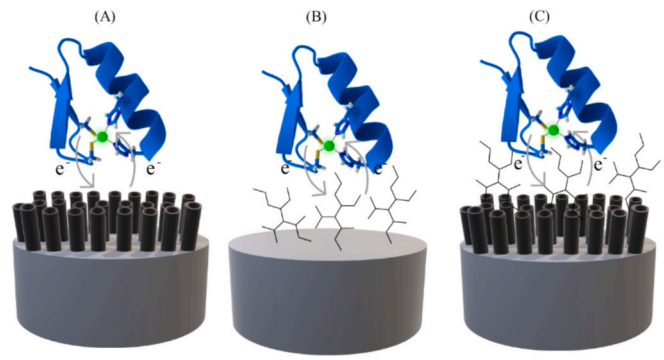

Fig. 1. Strategies to improve the sensitivity and specificity of electrochemical sensors in biosensing, including (A) the use of nanostructures, (B) the use of recognition elements, and (C) the combined nanostructure and recognition element strategies.

By modifying the electrode surface, the catalytic activity is improved accelerating the electron transfer while lowering the activation barrier of the electrochemical reaction, leading to an intensification of the signal and increased sensitivity of the sensor [170,171]. Nanocarbon, metal nanostructures, and recognition elements are crucial mechanisms to maximize the analytical performance of electrochemical sensors on the detection of zinc and zinc-containing proteins.

5.2. Nanocarbon-based strategies

Carbon materials are extensively used in electrochemical sensors due to their chemical inertness, wide potential window, low background current, affordability, and adaptability for various analyses [171,175,176]. These materials exhibit excellent electrochemical properties, high surface area, conductivity, biocompatibility, and improved interfacial adsorption [175,176]. Carbon-based electrodes have replaced toxic mercury electrodes in detecting zinc ions [177] and are used for Zn ion detection and metal-containing proteins. Various approaches, such as electrodepositing graphene oxide (GO) on glassy carbon electrodes (GCE) or solid-solid deposition of graphite powder on polyester films, have been explored for detecting Zn in environmental and biological fluids (Table 4).

Dias et al. developed flexible electrodes by applying graphite powder at high pressure (230 °C) on a thermal laminating sheet (Fig. 2). As a proof of concept, they evaluated the possibility of using the electrodes to determine the level of zinc present in sweat. The calibration curve showed a linear range of 50 to 2000 ppb, and a limit of detection (LOD) of 4.31 ppb [178].

Despite low LODs, like 5 $ng.ml^{-1}$ for graphene [177] or 4.31 $ng.ml^{-1}$ for flexible graphite electrode [178], these systems show limited specificity for Zn. To improve specificity, ion-imprinted polymers (IIP) with tailored binding sites have been utilized [180]. For example, 8-hydroxyquinoline and styrene on a glassy carbon electrode achieved a LOD of 0.06 $ng.ml^{-1}$ with a detection range of 0.06–0.12 $ng.ml^{-1}$. However, the narrow detection range limits its applicability in cancerous fluids. Researchers have functionalized carbon materials to selectively interact with zinc ions to enhance specificity, with bismuth often used to increase sensitivity and facilitate zinc ion deposition [181].

Nanocarbon-based electrodes have been extensively used for detecting metal-containing proteins. Structures like CNTs and graphene are ideal platforms for converting biorecognition events into electroanalytical signals [182]. A significant challenge in detecting these proteins is achieving effective electrical interaction between the protein's active site and the electrode, as the redox center is often insulated by the protein shell [182–184]. Direct electron transfer between proteins and electrode surfaces can be facilitated by either auxiliary mediators or nanostructures that anchor the active site to the electrode [182–185].

Table 4
Nanocarbon-based electrodes for zinc ion sensing.

Electrode	Solution	LOD (ng. ml^{-1})	Linear Range ($ng.ml^{-1}$)	Method	Limitations	Temperature	Interference analysis	Ref.
Reduced graphene oxide (ERGO) on GCE	Acetate buffer (pH 5)	5	50–3125	DPV	Low specificity	25 ± 1 °C	Selective to interfering ions, K(I), Cd(II), Mg (II), and Ca(II)	[177]
Graphite on polyester	Sweat	4.31	50 to 2000	ASV	Low specificity	25 ± 2 °C	Not mentioned	[178]
Highly aligned MWCNTs tower	Acetate buffer (pH 4.4)	12	Not informed	ASV	Low specificity	Not mentioned	Not mentioned	[179]
GCE-IIP	1 mM HCl (pH 3)	0.06	0.06 to 0.12	ASV	Low range of detection	25.0 ± 0.5 °C	4.5% decrease of the zinc response was observed in the presence of Ni, Co, Cd and Cu	[180]

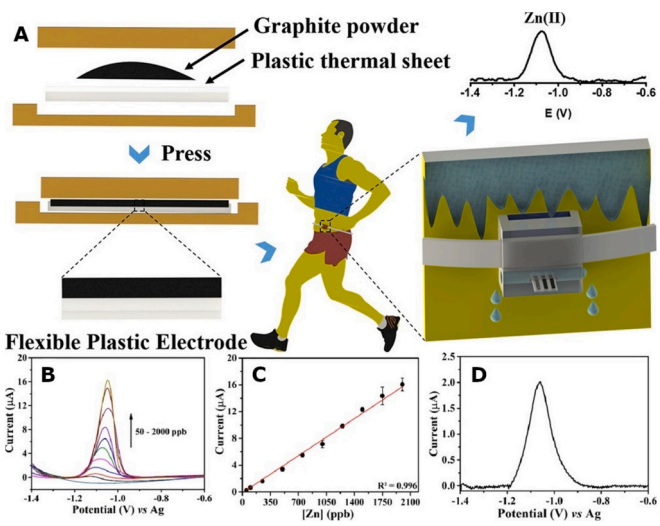

Fig. 2. a) Schematic illustrating the fabrication of the plastic-based wearable sensor and its application for sweat collection and subsequent zinc analysis. b) Square-wave voltammograms for varying zinc concentrations c) Calibration curve for zinc in the 50–2000 ppb concentration range. d) Square-wave voltammogram for real sample analysis using the wearable device. Reprinted (adapted) with permission from ACS Applied Materials & interfaces 2019, Dias et al., Environmentally Friendly Manufacturing of Flexible Graphite Electrodes for a Wearable Device Monitoring Zinc in Sweat. Copyright 2019 American Chemical Society.

Gupta et al. [184] explored the electron transfer capability of various nanostructured graphene forms—monolayer graphene, graphene oxide (GO), and reduced GO—toward iron-containing proteins. The study showed efficient electron transfer between graphene and the proteins' redox centres, without the need for mediators, while maintaining the proteins' structural integrity and biological activity. The edge defects and functional oxygen groups in the graphene supported protein interaction. Despite limited specificity, carbon nanostructures are notable for their ability to transfer electrons with buried redox centers, highlighting their potential as functionalized substrates in point-of-care sensors for detecting metal-containing proteins.

5.3. Nanometal-based strategies

Metallic nanoparticles enhance surface area and increase the mass transport rate, leading to faster electron transfer. Nanometals are widely studied for their sensitivity [186,187], with silver (Ag) and gold (Au) being the most commonly used for detecting heavy metals like cadmium (Cd), chromium (Cr), copper (Cu), lead (Pb), and zinc (Zn) [186,187] (See Table 5). Among all the popular candidates, those are the most popular due to their good biocompatibility and easy synthesis/modification [188]. In this context, as an example, AgNPs were used by researchers to develop an electrochemical modification-free biosensor for the sensitive detection of wild-type p53 protein, using in situ-formed AgNPs on an electrode surface as electroactive reporters for signal detection [189].

AuNPs are particularly popular for detecting metal-containing proteins [190,191]. Similar to carbon, AuNPs offer stable biomolecule immobilization while maintaining bioactivity and enabling direct electron transfer with protein redox centers without mediators [192,193]. Au nanostructures also improve electrode sensitivity and lower detection limits [187]. For instance, Shao et al. developed a polyaniline-multiwalled carbon nanotube (PANI-MWCNT) screen-printed electrode coated with electrodeposited AuNPs, which increased conductivity and surface area compared to PANI-MWCNTs alone. Using anodic stripping voltammetry (ASV), this system had a detection range of 1–180 $ng.ml^{-1}$ and a LOD of 39 $pg.ml^{-1}$ in ABS (pH 5) for real water samples [194]. Additionally, Au modified with titanium carbide and MWCNTs was used to detect zinc in urine and sweat 179. With antimony (Sb) as a co-deposition element, the system had a detection range of 350–830 $ng.ml^{-1}$ and a LOD of 1.5 $ng.ml^{-1}$ in acetate buffer (pH 4.6), and in biofluids, it showed responses for zinc concentrations from 200 to 600 $ng.ml^{-1}$ in urine and 50–1500 ng.ml-1 in sweat. Despite their high conductivity and surface area, the high cost and lower specificity of gold-based electrodes limit their clinical applications. However, AuNPs remain one of the most suitable metallic nanomaterials for functionalization and use as biosensor substrates.

Particularly for zinc ion detection, mercury (Hg) and bismuth (Bi) metal electrodes have been investigated in environmental and biological samples. Despite their toxicity, Hg electrodes are still used as a component to detect zinc due to their unique physicochemical properties and the wide cathodic potential window [177,195]. To overcome toxicity, in situ and ex-situ thin-film mercury electrodes (TFME) have been explored, aiming to decrease the Hg concentration and enable better electrode manipulation [177,196].

The in situ method, where Hg and the target metal are deposited simultaneously, has been widely used for metal detection. A notable example is the work by Ensafi et al. [197], who developed an in situ thin-film mercury electrode (TFME) on a carbon paste electrode for zinc detection in real water samples. This method achieved a detection range of 8–220 $ng.ml^{-1}$ and a LOD of 5.5 $ng.ml^{-1}$. Although the in situ approach improves electrode specificity, its application is limited in clinical settings due to the toxicity of mercury and challenges with co-deposition techniques.

To overcome these limitations, ex situ methods have been introduced as a safer alternative. In this approach, Hg nano/microdroplets are first deposited on the electrode surface, forming a thin film prior to immersion in the zinc-containing analyte. Oliveira et al. [198] developed a biochar-based Hg nanodroplet electrode to address this issue. Biochar, a highly functionalized carbon material derived from biomass and charcoal, exhibits excellent adsorption capabilities for ionic species such as Hg^{+2}. In their study, Hg^{+2} was electrodeposited onto the biochar carbon paste in an acetate buffer solution (pH 6) containing 1.0×10^{-4} M Hg^{+2}. When tested with anodic stripping voltammetry (ASV) in acetate buffer with varying zinc concentrations, the biochar-Hg system demonstrated a detection range of 20–3260 $ng.ml^{-1}$ and an LOD of 11 $ng.ml^{-1}$. The electrode was further evaluated using collyrium and ointment samples,

Table 5
Nanometal-based electrodes for zinc level sensing.

Electrode	Solution	LOD (ng. ml^{-1})	Linear Range (ng.ml^{-1})	Method	Limitations	Interference analysis	Temperature	Ref.
Au/PANI-CNTs	Acetate Buffer (pH 5)	0.039	1–180	ASV	High cost and lower specificity	Na(I), K(I), Ca(II), Mg(II), Cd(II), Co(II), Ni(II), Fe(II), Fe(III) and Hg(II)) had no significance	25 ± 2 °C.	[194]
Au/Ti-CNTs	Acetate buffer (pH 4.6)	1.5	350–830	ASV	Complex synthesis, co-deposition of Sb to increase sensitivity	Not mentioned	24 °C	[210]
Carbon-TFME	KNO_3/ HCl	5.5	8–220	ASV	High toxicity of mercury	Co^{2+}, Mn^{2+}, Mg^{2+}, Ca^{2+}, SO_4^{2-}, CO_3^{2-}, NO_3^-, NH_4^+ showed no effect	Not mentioned	[197]
Biochar-TFME	Acetate buffer (pH 5)	11	20–3260	ASV	High toxicity of mercury	Ni^{2+}, Cu^{2+}, Pb^{2+}, Cd^{2+}, and Fe^{3+} showed 7.0% variation at 10-fold lower concentrations	Not mentioned	[196]
Gold-BFE	Acetate buffer (pH 6)	1100	900–9000	ASV	Low sensitivity	Not mentioned	Not mentioned	[195]
Gold-BFE	Acetate buffer (pH 6)	11	180–4500	ASV	Complex synthesis	Not mentioned	Not mentioned	[203]
Bi-SPAuE	Acetate buffer (pH 5.5)	0.05	1–120	ASV	Limited range of detection	Small interferences from Pb(II), Cd(II), and Zn(II), larger interference from Hg^{2+}	Room temperature	[204]
GCE-BFE	Acetate buffer (pH 4.5)	1.02	5–110	ASV	In situ approach limits clinical application	Co(II), Ni(II), and Fe(III) ± 5% signal change	Room temperature	[200]
Graphene-PANI	Acetate buffer (pH 4.5)	1	10–300	ASV	Addition of in situ bismuth	Mn(II), Cu(II), Fe(III), Fe(II), Co(III), and Ni(II) showed no interference	Not mentioned	[181]
Fe_2O_3/ Graphene	Acetate buffer (pH 4.5)	0.11	1 to 100	ASV	Addition of in situ bismuth	Co^{2+}, Ni^{2+}, Mn^{2+}, Cu^{2+}, and Cr^{3+} 50-fold excess-signal changes varied from 2.31% to 8.46%	Not mentioned	[201]
C-ink on paper	Sweat and Serum	25	80 to 2000	ASV	Addition of in situ bismuth	Copper (1 ppm), iron (1 ppm), magnesium (20 ppm), lead (150 ppb), and nickel (5 ppb) showed no interferences	Not mentioned	[202]
C-Nafion-BFE	Acetate buffer (pH 4.6)	50	100–2000	ASV	Needs further studies to be used as portable sensor	Not mentioned	Not mentioned	[206]
Bi-Graphene	Acetate buffer (pH 4.6)	40	100–1600	ASV	Instability and large Bi structure	30 mM Na^+, 6 mM K^+, 59 μM uric acid, 0.12 μM Pb^{2+}, 0.02 μM Cd^{2+}, 0.42 μM Ni^{2+}, 5.2 mM Ca^{2+}, 9.8 μM Fe^{3+}, and 0.94 μM Cu^{2+} showed negligible interference	Not mentioned	[211]
Bi-Ti_3C_2	Acetate buffer (pH 4.5)	0.5	1–20	ASV	High cost, limited range of detection	100-fold concentration of K^+, Na^+, Ca^{2+}, Mg^{2+}, Ni^{2+}, Fe^{2+} and 50-fold concentration of Cu^{2+} showed negligible interference	Not mentioned	[207]
BDD-Bi	Acetate buffer (pH 5)	0.4	Not informed	ASV	High cost and in situ approach	Not mentioned	Not mentioned	[208]
BiCu-C	Acetate buffer (pH 4.5)	35	150–600	ASV	Complex synthesis	Ca^{2+}, Hg^{2+}, Cu^{2+}, In^{3+}, Cl^-, SO_4^{2-}, dopamine, ascorbic acid, and uric acid showed a variation of ±5% in signal change	Not mentioned	[209]

yielding comparable results to those obtained via the inductively coupled plasma (ICP) method. Despite the high sensitivity offered by mercury-based detection systems, the inherent toxicity of mercury severely limits their broader application, particularly in environmental and clinical settings. The development of alternative, non-toxic materials for metal ion detection remains a critical area for future research to enable safer and more widely applicable electrochemical sensing technologies [195].

Currently, the primary alternative to mercury for stripping techniques is the bismuth-modified electrode, which offers advantages like a reproducible voltammetric response, distinct stripping peaks, a more negative potential window, and a high signal-to-background ratio [199]. Bismuth is mainly applied as films on electrode materials, though nanostructured bismuth can also be utilized [187,195]. Electrodes can be prepared using both in situ and ex situ methods. Thanh et al. used bismuth's ability to form low-temperature alloys with heavy metals, co-depositing bismuth, and zinc on a glassy carbon electrode (GCE). Zinc detection via stripping voltammetry yielded a detection range of 5–110 ng.ml^{-1} and a LOD of 1.02 ng.ml^{-1} for zinc alone, increasing to 2.95 ng.ml^{-1} in the presence of other metals [200]. Other notable developments include graphene–polyaniline (G-PANI) nanocomposite electrode tested in buffer and serum, achieving a LOD of 1 ng.$ml^{-1}$and a detection range of 10–300 ng.ml^{-1}in buffer, and 10–50 ml^{-1} in serum [181]. Lee et al. developed a magnetic nanoparticle/graphene nanocomposite for GCE, detecting zinc with a LOD of 0.11 ng.ml^{-1} and a range of 1–100 ng.ml^{-1}[201]. Additionally, a carbon-ink screen-printed electrode on office paper was used for zinc detection in acetate buffer and biofluids, with a LOD of 25 ng.ml^{-1} and a detection range of 80–2000 ng.ml^{-1}[202].

While in situ bismuth deposition offers good detection limits, its clinical application is limited and ex-situ bismuth film method has emerged as a promising alternative. For instance, a miniaturized lab-on-a-chip sensor for zinc detection in serum was developed using ex situ deposited Bi film on a gold substrate, with a detection range of 0.9–9 μg/ml and a LOD of 1.1 μg/ml, though sensitivity was insufficient for clinical use [195]. By refining the fabrication process, the sensor was enhanced to achieve a detection range of 180–4500 ng.ml^{-1} and a LOD of 11 ng.ml^{-1} [203]. Li et al. further improved sensitivity by developing an ex situ Bi-gold electrode via Bi plating on screen-printed gold

electrodes, which showed a higher current response and a more defined voltammetric peak compared to in situ methods, with a detection range of 1–120 ng.ml^{-1} and a LOD of 0.05 ng.ml^{-1}[204] This enhanced sensitivity was attributed to the uniform growth of smaller bismuth particles, leading to better performance in real water samples. In addition, bismuth-based technology has been applied to monitor zinc in sweat using a wearable sensor. An ex situ Bi film was deposited on carbon ink with an auxiliary Nafion layer, successfully detecting zinc concentrations in sweat during exercise, with values consistent with the literature (Fig. 3) [205,206]. Another flexible graphene-based electrode, combined with structured bismuth deposition, detected zinc within a range of 100–1600 ng.ml^{-1} and achieved a LOD of 40 ng.ml^{-1}. These advancements highlight bismuth's potential for more sensitive and portable detection systems.

While effective in sweat detection, the design still requires improvements in stability, miniaturization of bismuth structures, and wireless real-time monitoring. These advancements could significantly impact clinical diagnostics and environmental monitoring by lowering detection limits. Bismuth's ability to detect trace zinc levels could aid in the early diagnosis of deficiencies or toxicities and enable more accurate environmental monitoring. However, the complexity of Bi fabrication and the need for further optimization remain challenges for practical, widespread application.

To further improve sensitivity, Bi has been combined with other metals such MXene (Ti_3C_2) nanosheets [207] and Boron-doped diamond (BDD) [208]. Bi-Ti_3C_2 layer offers ample active sites to form alloys with the target zinc metal during the cathodic reduction and offers a range of detection of 1–20 ng.ml^{-1} and LOD of 0.5 ng.ml^{-1}. Despite a very low LOD (0.4 ng.ml^{-1}), the biggest issue is the high cost and in-situ approach that limit its clinical applications. Cheaper alternative is the encapsulation of Bi and cupper (Cu) alloy nanoparticles (ANPs) in a flexible carbon film electrode [209]. This architecture improved the electrocatalytic activity and the acid resistance, while the carbon film assured the high electrical conductivity and fast electrochemical kinetics and effectively increased the active surface area of the electrode resulting in range of detection of 150 to 600 ng.ml^{-1} and LOD of 35 ng.ml^{-1}.

5.4. Recognition elements strategies

Using recognition elements is crucial for enhancing the specificity of electrochemical sensors. These elements, which can be bio or non-bio molecules, selectively interact with target species to generate an

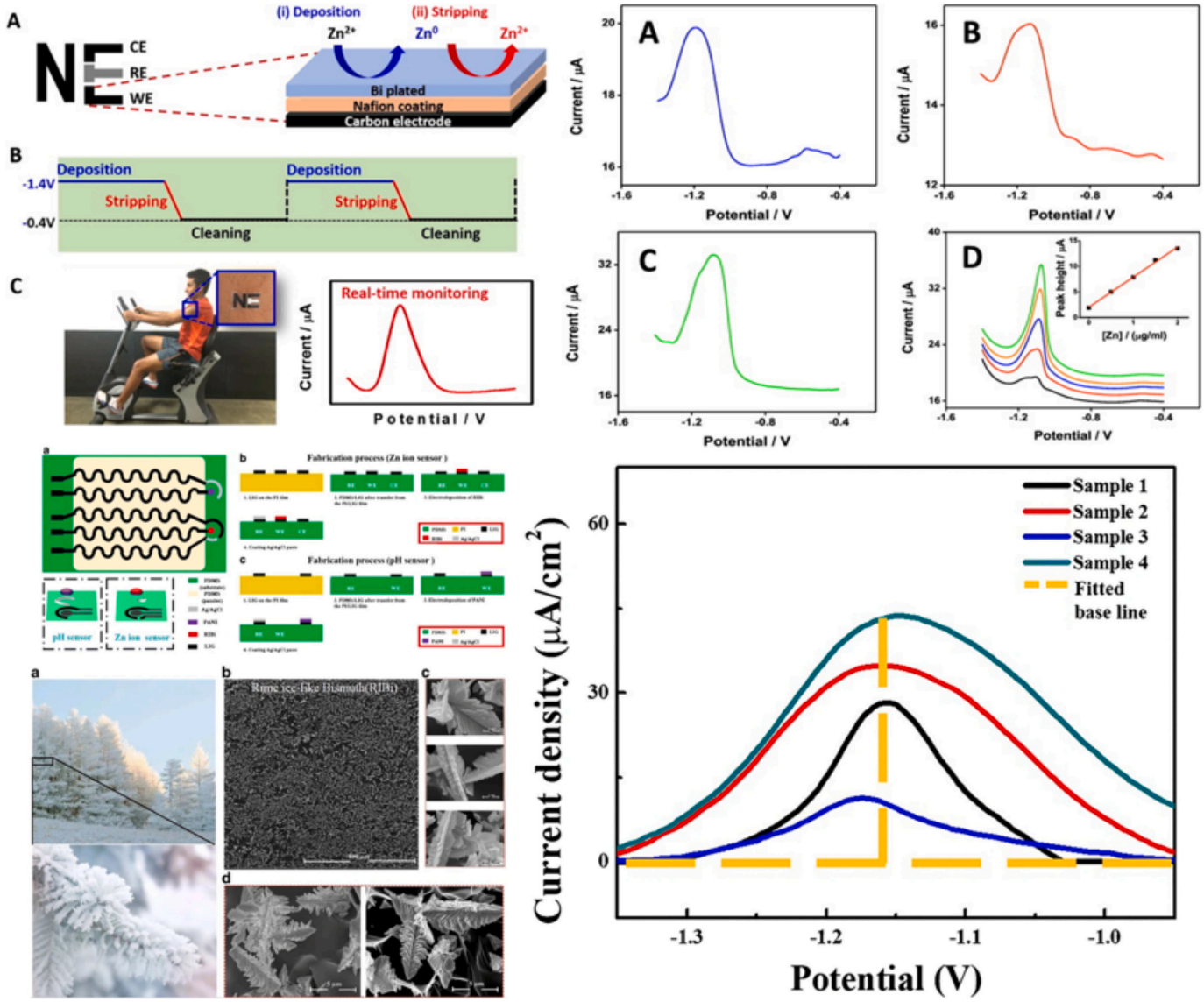

Fig. 3. Bismuth strategies: (a) A wearable temporary Bismuth-Carbon sensor designed to monitor zinc concentration in human sweat during exercise. Reproduced from ref. [206].

electrical signal related to the analyte's concentration [212,213]. Common recognition elements include enzymes [214–216], amino acids [217–219], peptides [218–220] and nucleic acids [221], as well as engineered bacteria [218,222,223], hormones [224,225] and small chemical molecules [218,226–229]. For metal-containing proteins, recognition layers typically use enzymes, antibodies, cells, nucleic acids, peptides, and aptamers [230]. Recognition elements can be integrated into electrochemical systems via label or label-free detection. The labeling approach involves chemically attaching a molecule to the target species to convert binding responses into electrical signals, requiring synthesis and purification [231]. The label-free method detects interactions directly through electrical signals, offering real-time detection [231,232]. While bio-recognition elements can enhance sensor specificity and sensitivity, issues such as shelf life, reliability, reproducibility, and high costs remain challenges [228]. The immobilization methods can reflect great differences in sensor sensitivity, stability, and performance [233]. The covalent attachment of biomolecules on the electrode surface is usually preferred due to its stability and reproducibility [233]. Combining recognition elements with nanostructures further addresses these issues by providing synergistic effects in catalytic activity, conductivity, and biocompatibility, leading to more sensitive biosensing [173,183,213,234]. Functionalized nanostructures are designed by immobilizing recognition elements on substrates using techniques like entrapment, adsorption, covalent bonding, or cross-linking [234].

5.5. Enzyme based sensors

Enzymes are highly effective in electrochemical sensors due to their specificity and catalytic efficiency, making them a common choice in sensor development. AuNPs and carbon-based electrodes are excellent substrates for enzyme loading [173,193]. Metal ions such as Zn^{2+} can interact strongly with enzymes, altering their active centers and reducing activity. These changes, such as variations in color, conductivity, and pH, can be indirectly measured through electrical signals [187,235]. For instance, glucose oxidase (GOx) was crosslinked on a carbon-poly (neutral red) film electrode to measure Zn concentration. The enzyme's activity in the presence of zinc varied and showed a detection range of 410 to 14,500 ng.ml^{-1} and LOD of 9 ng.ml^{-1}. The system successfully detected glucose in water, wine, and milk samples [214]. Another example utilized the unique interaction between collagenase and gelatin-coated gold electrodes to detect zinc-protein MMP-I. The system monitored impedance changes due to proteolytic digestion but was limited to very low collagenase concentrations (<2 mM) due to similar impedance levels at higher ionic strengths [236]. While enzymatic sensors offer high selectivity, their instability and sensitivity to microenvironmental factors pose challenges. One possible strategy to address these issues is redox cycling, which significantly improves the total signal by periodically cycling the electrochemical signal between the oxidation and reduction states. Nanozymes—which replicate the action of natural enzymes—have also been investigated because of their stability and simplicity of integration [228]. These limitations, however, have led to the development of non-enzymatic sensors, which offer simpler modification procedures and greater stability [173].

5.6. Immuno-sensors

Antibodies are highly advantageous for electrochemical sensors due to their high specificity and ability to recognize target molecules. Antibody-based sensors, or immunosensors, leverage the specific antigen-antibody (Ag-Ab) interactions to achieve high specificity and sensitivity [173,230]. There are two types of antibodies: polyclonal (pAb) and monoclonal (mAb). Polyclonal antibodies have multiple binding sites, whereas monoclonal antibodies have a single, high-affinity site. Monoclonal antibodies generally offer higher sensitivity compared to polyclonal antibodies [230]. Various substrates, including gold-based, carbon-based, and combined Au-Carbon electrodes, have been used for immobilizing antibodies on electrode surfaces. For instance, an immunosensor for MMP-9 was developed using AuNPs deposited on polydopamine-functionalized silica nanospheres (PDA/silica), followed by the adsorption of MMP-9 antibodies [237]. This design provided a high surface area, increasing the binding capacity and resulting in a detection range of 0.1 to 150 ng.ml^{-1} with an LOD of ng.ml^{-1}. The sensor was effective in serum samples, with results comparable to conventional ELISA assays. Another immunosensor for MMP-1 utilized a gold nanoparticle, polyethyleneimine, and reduced graphene oxide (AuNP/PEI/rGO) screen-printed electrode (SPE) [238]. Layers were assembled using mercaptopropionic acid and sulfur-gold bonding, and MMP-1 antibodies were immobilized through cross-linking. The system demonstrated a detection range of 1 to 50 ng.ml^{-1} and an LOD of 0.22 ng.ml^{-1}. This immunosensor was successfully applied in detecting MMP-1 in various biofluids, showing results comparable to ELISA. In another study, nitrogen-doped graphene (NG) nanostructures functionalized with AuNPs were used to adsorb horseradish peroxidase MMP-2 antibodies (HRP-Ab2) [239] (Fig. 4). This AuNPs-NG system increased the surface area for capturing MMP-2 and facilitated electron transfer, resulting in a detection range of 0.0005 to 50 ng.ml^{-1} and a LOD of 0.00011 ng.ml^{-1}. The performance was similar to ELISA assays in human plasma samples. Among these examples, signal amplification strategies also play an important role in improving the performance of immunosensors. These include enzyme-based amplification, such as the use of alkaline phosphatase, which catalyzes the conversion of substrates into electroactive products that can be detected electrochemically [240]. ALP-labeled immunosensors have shown enhanced sensitivity by amplifying the electrochemical signal even at low analyte concentrations [240,241]. Immunosensors are highly specific and sensitive to a wide array of analytes, including metal-containing proteins. However, there are still disadvantages related to these methods, such as high production costs. Dual-signal immunoassays, integrating both optical and electrochemical signals, are a promising approach to address these challenges [242]. The application of such dual-functional molecules and nanomaterials might overcome some critical limitations of antibody-based sensors by enhancing sensitivity, reliability, and cost-effectiveness [242]. Future advancements should focus on reducing costs, enhancing stability, and integrating advanced materials to improve performance and reliability. Continued innovation in electrode design and fabrication is essential for expanding these sensors' clinical applications.

5.7. Peptide-based sensors

To improve cost and shelf-life compared to antibodies and enzymes [243,244], peptide based sensors have been developed as recognition elements in the free-label detection of metal-containing proteins, especially MMPs [245–247]. The enzymatic cleavage of peptides on an electrode surface releases fragments that enhance electron transfer and increase current response [26]. However, the electrical response is often weak, requiring amplification [178]. Nanostructures are extensively used as signal amplifiers in peptide-based electrochemical sensors [243,248]. Peptide immobilization challenges and their single-use nature due to cleavage [244] are drawbacks. Peptides can be synthesized to target specific species and have a high affinity for metal ions due to their amino acid chains [249]. Liu et al. used a zinc-binding peptide (CCPGCGDGE) for zinc ion detection on an AuNPs-GCE surface [220]. The AuNPs-GCE, prepared with poly-diallyl dimethylammonium chloride, was incubated with zinc solutions and peptide and then treated with mercaptohexanol. EIS detected Zn^{2+} in the range of 1.4 to 68 ng.ml-1 with a LOD of 0.68 ng.ml-1, showing good performance in urine samples. Oxytocin, a peptide hormone, is used for zinc detection due to its binding properties. Mervinetsky et al. created a zinc-selective oxytocin sensor by coupling oxytocin with COMU reagent on a lipoic acid-treated gold surface [224]. The oxytocin terminal amine was linked

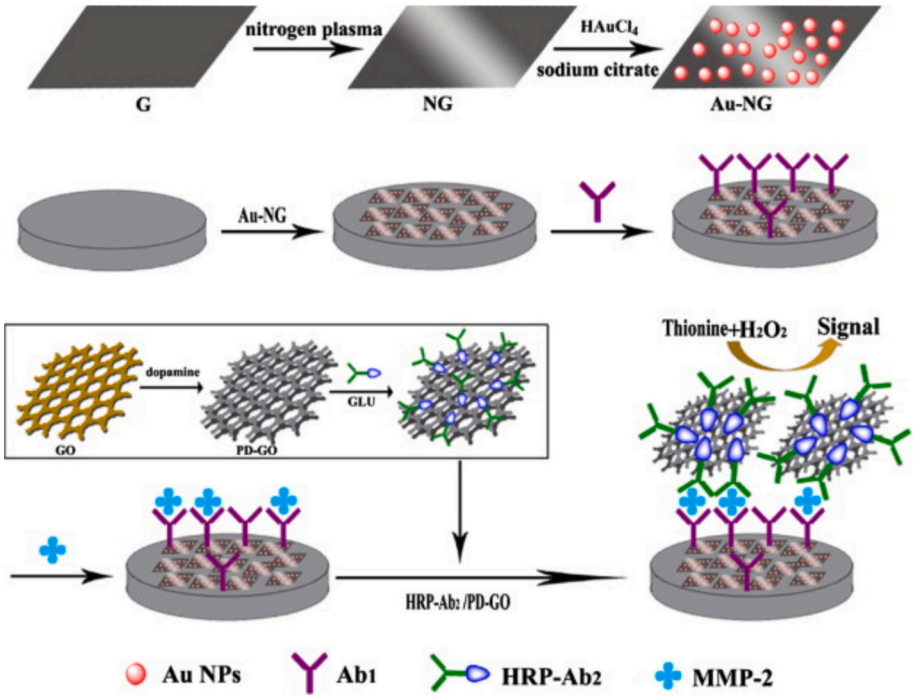

Fig. 4. Schematic illustration of the fabrication of an ultrasensitive electrochemical immunosensor based on a signal amplification strategy for the detection of MMP-2. Reproduced from ref. [239].

to the lipoic acid layer, avoiding copper ion binding. The sensor had a detection range of 0.01 ng.ml-1 to 20 µg.ml-1, eliminating affinity for other metals. This innovative work provided a new tuning strategy for the target ion binding by peptides in which the affinity toward other metals could be eliminated by inactivating a specific binding site. A peptide-decorated AuNPs and CNTs electrochemical sensor was designed for MMP-7 detection [243]. CNTs were deposited on gold electrodes before AuNP electrochemical deposition. Peptide (JR2EC) was immobilized using gold-thiol chemistry. The sensor, evaluated by DPV in PBS solution with K4[Fe(CN)6]4−/3- (pH 7.4), detected MMP-7 in the range of 0.01 to 1000 ng.ml-1 with an LOD of 0.006 ng.ml-1, showing potential for clinical use. Another strategy involved peptide-coated hydrogel film degradation by MMP-9 [250] (Fig. 5). Cysteamine was drop-coated on interdigitated gold electrodes, followed by cross-linking with MMP-9-specific peptides. EIS monitored film degradation to detect MMP-9 activity in the concentration range of 50 to 400 ng.ml-1 with an LOD of 15 ng.ml-1.

Peptide-based sensors for zinc biomarkers offer a cost-effective and versatile approach with impressive sensitivity and specificity. Advances in peptide synthesis and nanostructure integration have enhanced detection capabilities, making these sensors suitable for various applications, including clinical diagnostics. Future developments could focus on improving sensor stability and multiplexing capabilities to broaden their applicability in complex biological samples. Overall, peptide-based sensors hold significant promise for precision medicine and targeted biomarker detection.

5.8. Oligonucleotide-based sensors

The interaction between nucleic acids and metallic ions has been explored as a recognition element in electrochemical zinc detection, offering high specificity and sensitivity. For example, a paper-based sensor using reduced graphene oxide (rGO), iron-porphyrinic MOF ((Fe—P)n-MOF), and G-quadruplex-hemin was developed for on-site applications such as environmental monitoring, food safety, and disease diagnosis [221]. This system had a detection range of 0.02 to 950 ng.ml^{-1} and a LOD of 4 pg.ml^{-1}, proving effective in HepG2 cell extracts

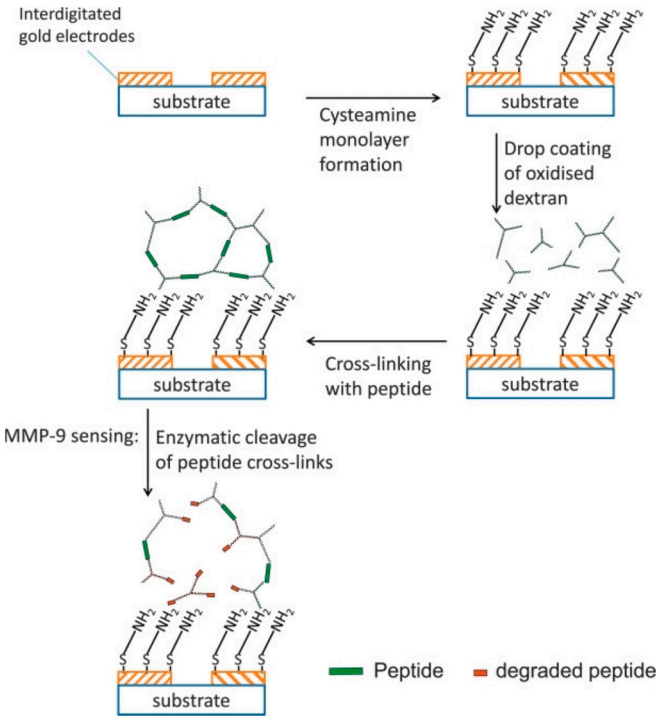

Fig. 5. A schematic of the sensor coating process including a two step-coating method adopted to deposit MMP-9 sensitive films. Reproduced from ref. [250].

and water samples. In another study, AuNP-decorated graphene electrodes were functionalized with lung cancer DNA sequences for p53 detection [251]. The DNA-graphene-AuNP surface was incubated with a p53 antibody for 1 h and p53 biomarker was detected at a range of 0.0001 to 0.1 ng.ml^{-1}, and a LOD of 0.006 pg.ml^{-1}. Aptamer-based sensors, a promising new approach, are designed for high affinity and stability toward target species, including metal ions and organic

molecules [230]. Although aptamers offer better stability and easier immobilization compared to antibodies, their rapid degradation, complex synthesis, and lack of standardized protocols can limit their application as point-of-care devices [252,253]. An aptamer-based sensor for MMP-9 and MMP-2 was developed using thiol–pyridyl disulfide exchange [254]. Gold electrodes modified with chemical vapor-deposited graphene were treated with pyrene-pyridinyl disulfide (PSE) and aptamer solutions. This aptamer-based sensor achieved LODs of 0.0092 $ng.ml^{-1}$ for MMP-9 and 0.95 $ng.ml^{-1}$ for MMP-2. Another example is the sensor developed by Ansari et al., who used aptamers immobilized on a hybrid nanostructure made of graphitic carbon nitride, zirconium dioxide, and multiwalled carbon nanotubes for the detection of MMP-9 in human serum and saliva [255]. This sensor exhibited a wide range of detection between 50 and 1250 $pg.ml^{-1}$ and an excellent LOD of 10.51 $pg.ml^{-1}$. The working principle of the sensor is presented in Fig. 6.

These high specific and versatile sensors represent a powerful evolution in detection technology. The integration of novel materials and structures, such as graphene and aptamers, has markedly improved sensor performance in various applications. Future research should aim to enhance the stability and ease of synthesis of these nucleic acid-based components to further expand their utility in real-world settings.

5.9. Organic compound-based sensors

As previously mentioned, the use of nanostructures can enhance sensitivity and specificity for targeting zinc-related biomarkers in biofluids, but limited shelf-life, complexity, and high cost remain. In contrast, non-biological recognition elements could offer lower costs, longer shelf-life, inherent stability, and comparable sensitivity and specificity [256]. Teng et al. [226] functionalized exfoliated graphite (EG) with zincon, a molecule known for its strong zinc ion complexation ability. By utilizing π-π interactions, zincon was conjugated with EG and applied to screen-printed electrodes (SPE) for detecting mobile zinc ions in early prostate cancer diagnosis. The system achieved a LOD of 5 $ng.ml^{-1}$ and a detection range of 250 to 1500 $ng.ml^{-1}$. However, the system showed lower sensitivity (2500 $ng.ml^{-1}$) when tested with serum samples from mouse prostate cancer. Vieira et al. [257] used zincon-modified CNTs for rapid and reliable detection of free zinc ions in artificial urine and saliva (Fig. 7). Electropolymerizing zincon on CNTs enhanced stability and sensitivity. Using square wave voltammetry (SWV), the zincon-CNT system specifically quantified mobile Zn^{2+} in salivary and urinary matrices with a sensitivity of approximately 100 $ng.ml^{-1}$ and an LOD of about 20 $ng.ml^{-1}$.

An emerging strategy in electrochemical detection of metal-containing proteins involves using organic inhibitor molecules that react with proteins, causing changes in the electrochemical response. Moradi et al. [258] monitor on GC electrode the current signal of CA interaction with three different inhibitory drugs: acetazolamide, dorzolamide, and methazolamide. Methazolamide proved to be the most effective inhibitor, and it was used to measure CA concentration. This inhibitory strategy showed a current response for CA concentrations ranging from 0 to 600 $ng.ml^{-1}$, with an LOD of 6 $ng.ml^{-1}$, and maintained stability over 3 months. Vieira et al. [259] employed bismuth nanomaterials tethered to mesoporous carbon via a conductive spacer arm to measure CA using stripping analysis. The zinc finger metalloprotein biosensor detected increased concentrations of metalloproteins in saliva, displaying high specificity, sensitivity, repeatability, and an LOD of 11 $ng.ml^{-1}$ for CA metalloprotein. Vieira et al. [260] developed a novel approach to detect MMP-14 by targeting the hemopexin (PEX) domain of the protein instead of the catalytic domain (Fig. 8**)**. They covalently grafted the stable and low-cost molecule NSC-405020 onto the surface of carbon nanotubes. NSC-405020 specifically binds to the PEX domain of MMP-14. EIS was used to detect and quantify MMP-14, showing a linear detection range of 10 to 100 $ng.ml^{-1}$and an LOD of 7.5 to $ng.ml^{-1}$. The specificity of NSC-405020 was even validated against the PEX domain of MMP-1.

Table 6 lists and summarizes some of the existing studies using different recognition elements, such as the ones mentioned before, for

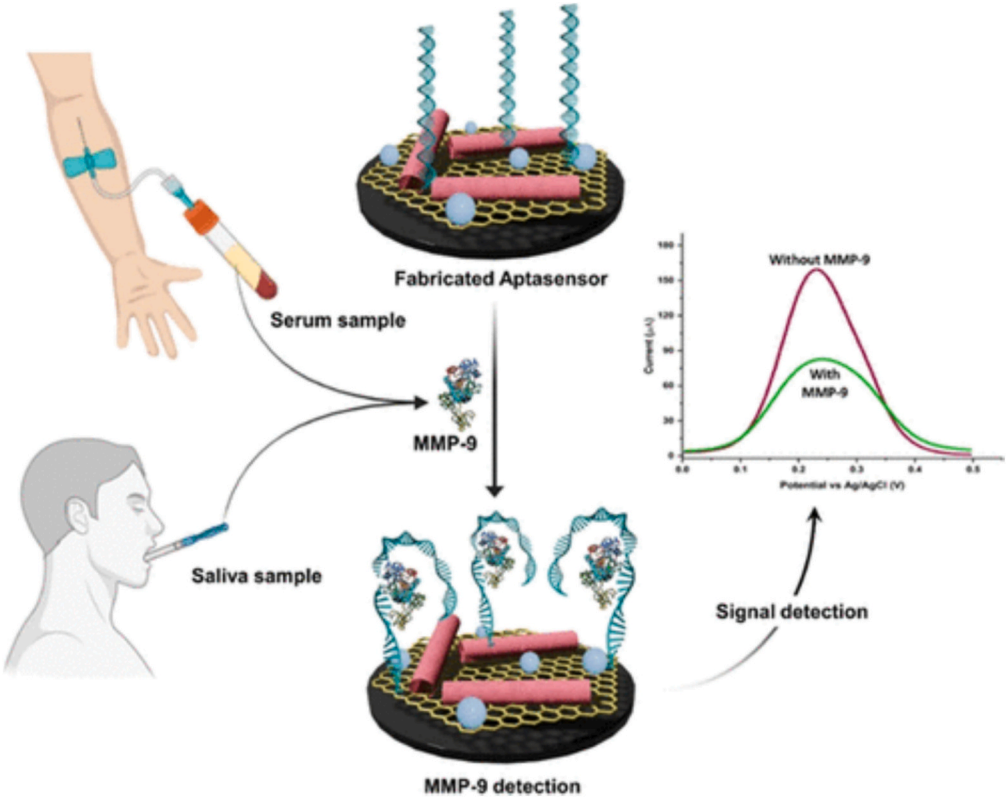

Fig. 6. Reprinted with permission from [255]. Copyright 2024 American Chemical Society. Functioning of the biosensor developed by the authors.

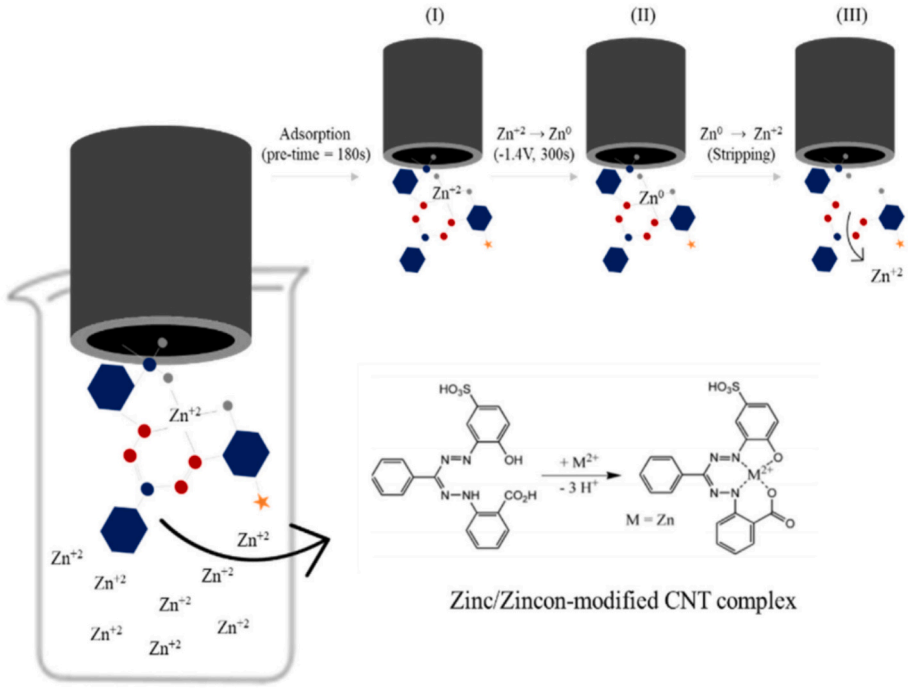

Fig. 7. Schematic representation of the complexation mechanism between zincon-modified CNT and Zn + 2, involving: (I) adsorption, (II) reduction, and (III) stripping steps. Reproduced from ref. [257].

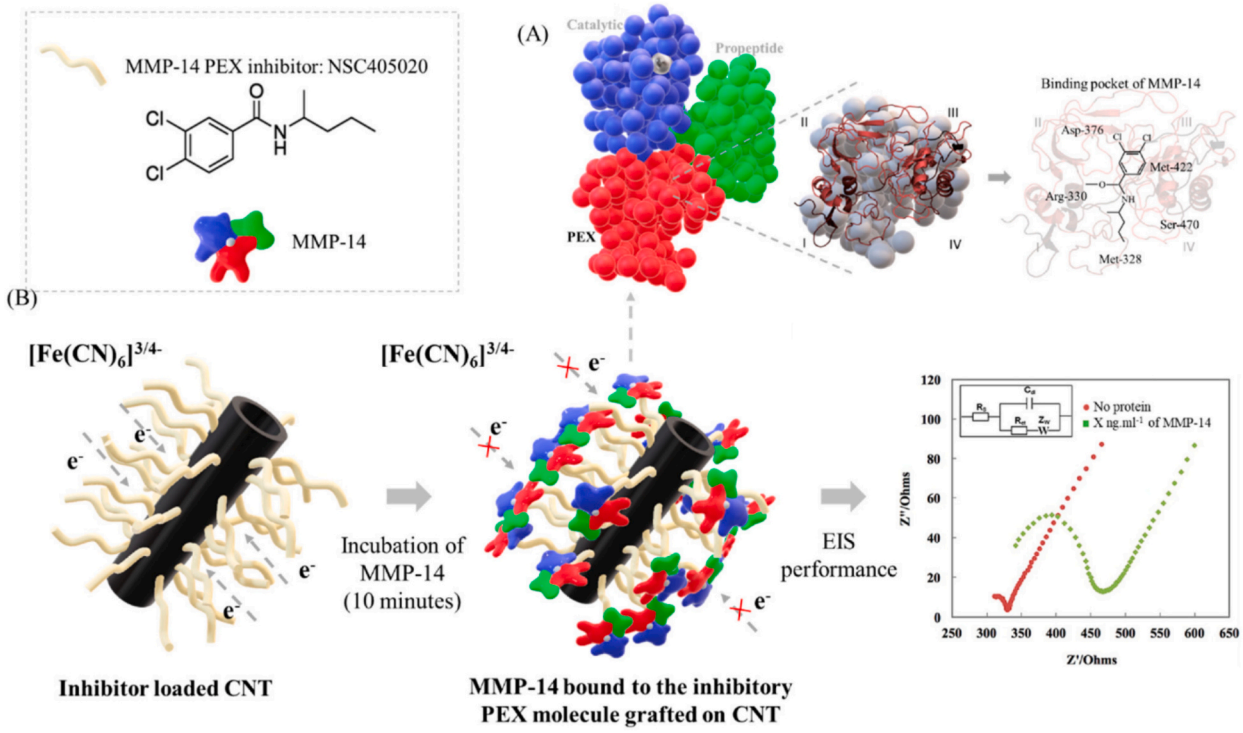

Fig. 8. (A) The interaction between the inhibitor NSC 405020 and the binding pocket of MMP-14 protein, and (B) a schematic illustrating the detection of MMP-14 via the binding mechanism between the protein and the inhibitory small molecule as the recognition element. Reproduced from ref. [260].

the detection of zinc ions and zinc-containing molecules. The integration of organic compounds with advanced nanostructures offers significant advancements in the detection of zinc-related biomarkers and metal-containing proteins. These approaches address key challenges such as cost, stability, and sensitivity, enabling more accessible and reliable diagnostic tools.

6. Conclusion and future perspectives

The present review described the recent innovations in the field of electrochemical detection of zinc-related biomarkers present in cancer-related fluids. Different strategies for improving the sensitivity and selectivity of electrochemical sensors toward quantitative detection of

Table 6
Recognition of elements-based electrodes for zinc level sensing.

Electrode	Recognition element	Analyte	Solution	LOD (ng. ml^{-1})	Range (ng. ml^{-1})	Method	Limitations	Ref
Carbon-GOx -Poly(red) film	Enzyme	Zinc ion	PBS (pH 7.0)	9	410 to 14,500	Chrono-amperometry	Low range of detection for biofluids	[214]
MMP-9 antibody on AuNPs-PDA-Silica	Antibody	MMP-9	KCL in Fe $(CN)_6]^{3-/4-}$(pH 7.0)	0.06	0.1 to 150	CV	High cost of antibodies	[237]
MMP-2 antibody on AuNPs-rGO	Antibody	MMP-2	PBS (pH 7.4)	0.00011	0.0005 to 50	DPV	High cost of antibodies and limited range of detection	[239]
MMP-1 antibody on AuNP/PEI/rGO	Antibody	MMP-1	PBS (pH 7.4)	0.22	1 to 50	DPV	High cost of antibodies and limited range of detection	[238]
GCE-AuNPs- CCPGCGDGE	Peptide	Zinc ion	KCL in Fe $(CN)_6]^{3-/4-}$	0.68	1.4 to 68	EIS	Limited range of detection	[220]
Au-Oxytocin	Peptide (Hormone)	Zinc ion	KCL in Fe $(CN)_6]^{3-/4-}$	Not informed	0.01 to 20.000	EIS	Needs validation in biofluids	[224]
CNT-AuNPs-Peptide	Peptide	MMP-7	PBS (pH 7.4)	0.006	0.01 to 1000	DPV	One-time use and fluctuation on the signal	[243]
Au/Peptide/Dextran	Peptide	MMP-9	Tris-buffer (pH 7.5)	15	50 to 400	EIS	Complex synthesis, one-time use	[250]
Fc-CMCS hydrogel sensor	Peptide	MMP9	PBS (pH 7.4)	73.08	50–1000	DPV	Needs validation in biofluids	[261]
rGO-MOF-G-quadruplex	Nucleic Acid	Zinc ion	PBS (pH 7.0)	0.004	0.02 to 950	DPV	Complex synthesis	[221]
AuNP-decorated graphene-DNA	Nucleic Acid	p53	PBS (pH 7.4)	0.000006	0.0001 to 0.1	EIS	Limited range of detection for biofluids	[251]
ERGO-IDE	Aptamer	MMP-2	PBS (pH 7.0)	0.00332	0.01–10	EIS	Needs long-time stability tests	[262]
u-decorated boron nitride nanotubes	Aptamer	MMP9	Human serum	0.0218	0.1–10,000	EIS, CV	Complex synthesis	[263]
Au-Graphene-PSE	Aptamer	MMP-9 and MMP-2	PBS (pH 7.4)	0.0092 and 0.95	Not informed	DPV	Complex synthesis	[254]
g-C3N4-NS/MWCNTs/ZrO2-NPs/chitosan nanocomposite	Aptamer	MMP9	Not informed	0.01051	0.05–1.25	DPV	Limited range of detection	[255]
Functionalized Zincon-graphite SPE	Non bioelement	Zinc ion	Tris HCl buffer (pH 7.5)	5	250 to 1500	DPV	Low sensitivity in serum samples	[226]
Zincon-modified CNTs	Non bioelement	Zinc ion	Artificial urine and saliva	20	125 to 1000	SWV	Needs validation in biofluids	[257]
Zincon-MoS_2 modified GCE	Non bioelement	Zinc ion	PBS (pH 7.5)	59	Not informed	CV	High limit of detection	[264]
GCE	Non bioelement	Carbonic anhydrase	TBS buffer (pH 7.4)	6	0–600	Chrono-amperometry	No nanostructured surface was studied.	[258]
Bismuth-Sulfonated Carbon	Non bioelement	Carbonic anhydrase	PBS (pH 6.0)	11	50–500	SWV	High limit of detection in saliva	[259]
NSC-405020 -CNT	Non bioelement	MMP-14	PBS (pH 7.40) + $Fe(CN)_6]^{3-/4-}$	7.5	10–100	EIS	Needs validation in biofluids	[260]

zinc and zinc-containing proteins are available in a variety of environmental and biological fluids. Functionalized nanostructured materials demonstrated an incredible ability to boost sensors' performance with fast, accurate, and sensitive detection of zinc-related biomarkers. A detailed analysis has confirmed that the sensitivity of electrochemical sensors can be significantly superior through various design strategies, including the use of nanocarbon, nanometal, and recognition elements on the electrode surfaces. However, further development in this research field must be made to be able to address the major challenges, including i) satisfactory stability and controlled synthesis of sensors' surfaces; ii) proper immobilization of recognition elements on nanostructures; iii) design of novel non-bio recognition elements-based electrodes; iv) better sample validation, including biofluids not only buffer solutions; v) cross interference within the similar elements present in biofluids; vi) real clinical scenario validation; and vii) storage capability. In addition, it is essential to better understand the electrochemical behavior in the complex biological samples, such as serum, urine, and saliva. The translation of electrochemical systems presenting high sensitivity and specificity to the clinical practice is still a challenge because of the nonspecific adsorption of numerous biomolecules present in the biofluids at the electrode surface. This can drastically block the electrochemical signal, increasing the background noise and decreasing the specificity of the sensor. The use of nanostructures it is one of the strategies in place to overcome biofouling, however, if it is not sufficient, few directions must be conducted as the design of polymer antifouling layers, nano porous membranes, and hydrogels. Furthermore, the miniaturization of electrochemical sensors to desirable portable devices may be developed through efficient connectivity and integration between distinct areas of research, ensuring large scale production, accessibility, and cost reduction.

CRediT authorship contribution statement

Daniela Vieira: Writing – original draft, Methodology, Data curation, Conceptualization. **Graziele Cruzado:** Writing – original draft, Data curation. **Edward Harvey:** Writing – review & editing. **Geraldine Merle:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

There are no conflicts to declare.

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Data availability

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

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