



Molybdenum disulfide based nanohybrids: insights into their role in electrochemical cancer biomarker detection

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Abstract

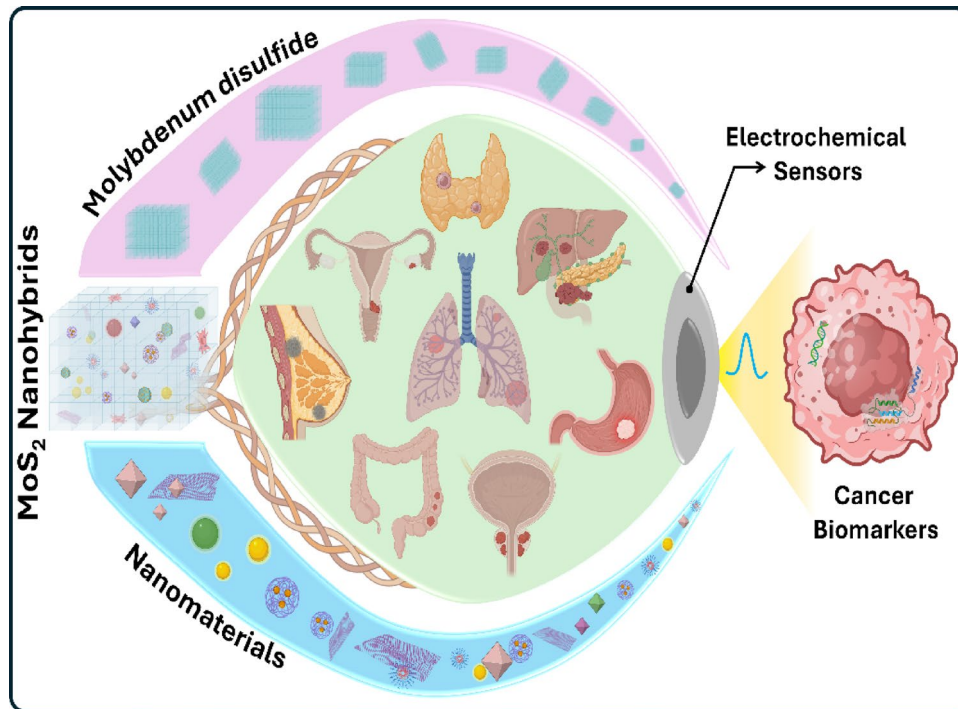
Cancer remains a leading cause of global mortality, where early detection and continuous monitoring are critical for improving therapeutic outcomes. However, conventional diagnostic techniques suffer from high cost, long assay times, invasiveness, and limited sensitivity at early disease stages. In this context, electrochemical biosensors have emerged as promising alternatives due to their rapid response, cost effectiveness, low sample volume requirements, high sensitivity, and compatibility with point-of-care testing. Recent advances highlight the pivotal role of electrode materials in translating biomolecular recognition into reliable electrical signals, particularly for detecting cancer-associated biomarkers near clinically relevant threshold levels. Among emerging semiconducting materials, molybdenum disulfide (MoS_2) has attracted significant attention owing to its layered two-dimensional structure, tunable bandgap, abundant electroactive edge sites, and versatile surface chemistry. This review critically examines recent progress in MoS_2 nanohybrid based electrochemical biosensors for cancer detection, focusing on material design strategies, fabrication approaches, and biomarker-specific sensing architectures. Emphasis is placed on MoS_2 hybrid systems incorporating carbon nanostructures, metal nanomaterials, metal oxides, polymers, MOFs, and other nanostructures, as well as their roles in enhancing signal transduction and real-time applicability in clinical samples. Finally, current challenges are outlined towards developing clinically translatable electrochemical sensing systems for early cancer detection and disease diagnosis. Furthermore, this review highlights the potential of integrating semiconductor-based electrochemical sensors with threshold-based diagnostic strategies as a promising future direction for point-of-care cancer detection.

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Graphical abstract



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1 Introduction

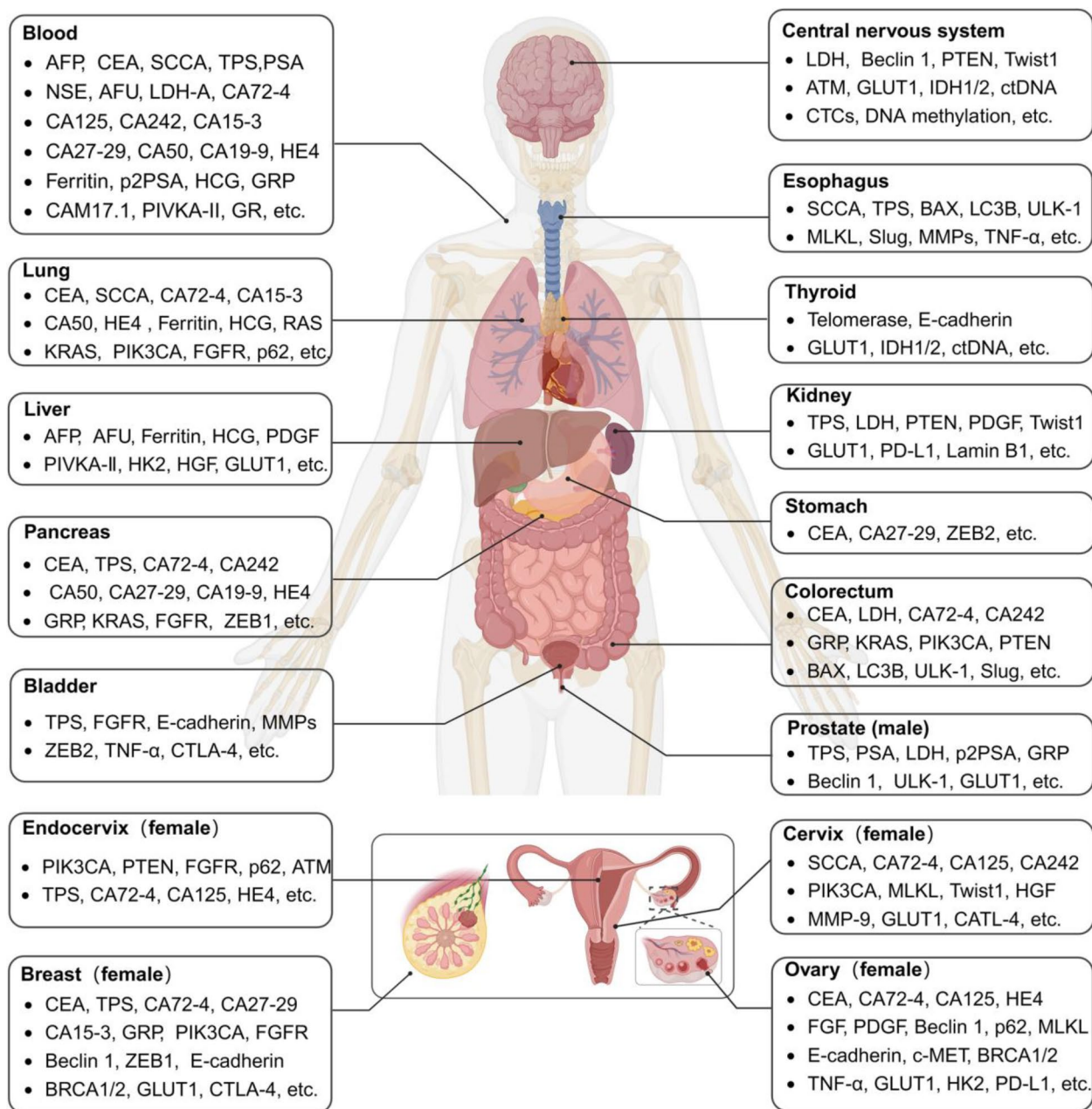
Cancer continues to be one of the most critical global public health challenges of the 21st century. In 2022, about 20 million new cases were diagnosed worldwide, with nearly 9.7 million deaths attributed to the disease [1, 2]. The most common and deadly types include lung and breast cancer, with approximately 2.48 million lung and 2.30 million breast cancer cases in 2022. Lung cancer remained the leading cause of cancer-related mortality, causing around 1.82 million deaths, nearly one-fifth of all cancer deaths [3]. Projections indicate that by 2050, the global cancer cases could reach about 35 million annually, a 77% increase, with deaths rising correspondingly [4]. Effective cancer management relies on early detection and accurate staging. However, many cancers are undetected at early stages because they remain asymptomatic until late, and clinical thresholds for detection are usually met only after substantial tumor growth. Traditional diagnostic tools like imaging and tissue biopsies remain the clinical standard but are costly, invasive, and less effective for early detection [5, 6]. Newer approaches, such as liquid biopsies, biomarker-based assays, and AI-enhanced diagnostics, offer non-invasive, real-time, and increasingly sensitive alternatives by analyzing circulating tumor DNA (ctDNA), circulating tumor

cells (CTCs), exosomes, and cancer-specific molecular signatures [7]. Despite their promise, these methods still face challenges related to sensitivity, clinical validation, high cost, accessibility, and data standardization.

Moreover, the widening diagnostic gap has increased global focus on biomarker-based cancer detection, which aims to identify molecular signatures released, shed, or altered during tumor development. Cancer cells release a variety of biomarkers, including proteins, nucleic acids, metabolites, lipids, CTCs, extracellular vesicles, and exosomal cargo, detectable in accessible fluids like blood, saliva, urine, sweat, and exhaled breath [8, 9]. Since these biomarkers reflect underlying disease changes well before tumors are visible on scans, they offer great potential for early, minimally invasive diagnosis, monitoring treatment responses, and predicting recurrence or metastasis. Cancer biomarkers, classified as tumor-specific or tumor-associated, play essential roles in diagnosis, prognosis, and therapy selection across cancers. Tumor-specific markers such as human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS), BRAF, BRCA1/2, and microsatellite instability-high (MSI-H) inform targeted treatments by mapping oncogenic pathways, while tumor-associated markers, including prostate specific

antigen (PSA), cancer antigens CA-125, CA-19-9, CA15-3 and carcinoembryonic antigen (CEA), support screening and disease monitoring [10–12]. Protein biomarkers such as PSA, CA15-3, CA19-9, CEA, alpha fetoprotein (AFP), and CA125 indicate prostate, breast, pancreatic, colorectal, liver, and ovarian cancers, respectively [13]. Nucleic acid biomarkers like circulating microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and ctDNA provide genetic and epigenetic information on tumor heterogeneity and drug resistance [14]. Small molecules like homovanillic acid

(HVA), trimethylamine N-oxide (TMAO), sarcosine, choline, and oxidative stress markers such as H_2O_2 give additional biochemical insights into cancer metabolism [15]. A comprehensive list of tumor biomarkers [16] is displayed in Fig. 1. These biomarkers are often detected at very low concentrations (pM to fM levels) in early stages, and their stability varies in biological fluids, presenting significant analytical challenges. Their detection relies on diverse technologies like polymerase chain reaction (PCR), sequencing, immunoassays, mass spectrometry, CRISPR-based



Overview of human tumor biomarkers

Fig. 1 A comprehensive overview of various tumor biomarkers. Reproduced with permission from [16]

platforms, radioimmunoassay, and advanced imaging, providing sensitive, multi-layered, diagnostic capabilities that increasingly enable personalized, pathway-oriented cancer management [17, 18]. Even though techniques like ELISA, mass spectrometry, qPCR, and next-generation sequencing have significantly advanced biomarker research, yet they face challenges in standard clinical tests. Also, these traditional methods often involve multiple steps, complex sample preparation, expensive equipment, skilled operators, and long processing times, limiting their use for broad screening, especially in resource-scarce areas [19, 20]. Additionally, biomolecules in biofluids are embedded in complex matrices filled with interfering proteins, salts, and metabolites, posing issues such as signal suppression, nonspecific binding, enzymatic breakdown, and low biomarker levels. On the other hand, detecting short RNA molecules like miRNAs with high similarity also requires high specificity that many assays cannot deliver [21]. These challenges underscore the urgent need for rapid, sensitive, selective, and portable detection methods that can accurately measure trace-level cancer biomarkers in complex biological samples. This has driven the innovation of new sensing technologies, especially electrochemical biosensors, which are well-suited to overcome many limitations of traditional diagnostics.

Electrochemical sensors, in their broadest form, have long been recognized for their exceptional analytical capabilities, owing to their direct and efficient conversion of chemical and biochemical events into electrical signals [22]. These devices operate on well-established electroanalytical principles such as voltammetry, amperometry, potentiometry, and impedance spectrometry, which provide high sensitivity, precise quantification, and rapid response kinetics [23]. One of the key strengths of electrochemical sensing is its inherent scalability and simplicity, where it is compact, inexpensive, and easily miniaturized, allowing integration into portable, wearable, implantable or disposable platforms [24, 25]. Their low power requirements, compatibility with microelectronics, and ability to function in turbid or optically opaque samples make them versatile across environmental, biomedical, food, and industrial applications [26]. Electrochemical sensors also offer remarkable detection sensitivity, often at nM to fM levels, because the signal arises directly from electron-transfer processes at the electrode interface. Unlike optical methods that require labels, skilled technicians, and complex instrumentation, electrochemical sensing maintains a high signal-to-noise ratio even in miniaturized formats [27, 28]. Importantly, these sensors require minimal sample volumes, operate effectively in complex media, and allow real-time and continuous monitoring, making them ideal for point-of-care systems that

demand rapid turnaround and on-demand measurement [29, 30].

To add to these advantages, electrochemical biosensors extend the capabilities of classical electrochemical sensors by integrating biorecognition elements such as antibodies, aptamers, nucleic acids, peptides, enzymes, or molecularly imprinted polymers (MIPs) onto the electrode surface [31, 32]. This functionalization imparts biomolecular specificity while preserving the sensitivity and rapid responsiveness of the underlying electrochemical transducer [33]. In the context of disease diagnostics, especially cancer detection, its hybrid design enables selective recognition of tumor-derived biomarkers, including proteins, circulating nucleic acids, metabolites, exosomal components, and reactive species. Many cancers release biomarkers at extremely low concentrations during early development, well before imaging modalities or clinical symptoms become evident [34]. Electrochemical biosensors, with their high sensitivity and rapid response, are ideally suited for detecting these subtle molecular fluctuations [35]. Furthermore, the ability to operate with small sample volumes often from serum, saliva or urine facilitates minimally invasive early screening and their compactness, low cost, and compatibility with point-of-care and wearable devices address key limitations of conventional diagnostics [36, 37]. Crucially, electrochemical biosensors can be readily adapted to multiplex detection, enabling parallel measurement of multiple biomarkers, which is an essential requirement for cancers that lack a single signature marker and instead rely on diagnostic panels. As a result, electrochemical biosensors are emerging as a powerful technology platform capable of delivering fast, sensitive, selective, and decentralized cancer diagnostics, aligning with global goals for early detection and improved patient outcomes [38, 39]. The performance of electrochemical biosensors ultimately depends on the electrode material, which governs electron-transfer efficiency, bioreceptor stability, and overall signal quality [40]. Bare electrodes often provide limited surface area and poor biomolecule binding, prompting extensive research into engineered sensing interfaces. Various material classes have been explored, including noble metals for conductivity and biofunctionalization, carbon nanomaterials for large surface areas and fast charge transport, conducting polymers for biocompatible and anti-fouling films, and metal oxides or organic frameworks for catalytic and porous architectures [41–44]. While each contributes unique advantages, recent attention has increasingly shifted toward semiconducting nanomaterials, which offer tunable band structures, high surface-to-volume ratios, and strong sensitivity to interfacial biochemical changes. These features make semiconductors exceptionally responsive to low-abundance cancer biomarkers [45].

Among semiconducting materials, molybdenum disulfide (MoS_2) has gained prominence because of its unique combination of structural and electronic attributes. Its 2D layered S-Mo-S architecture provides a large electroactive surface with a high density of exposed edge sites that actively participate in redox processes [46]. The material exhibits a tunable bandgap, transitioning from indirect in bulk to direct in monolayer form, which enhances its electron-transfer kinetics and responsiveness to interfacial binding events [47]. MoS_2 also offers excellent chemical stability, mechanical flexibility, and strong affinity for biomolecules, allowing efficient immobilization of antibodies, aptamers, DNA probes, or MIPs. Additionally, its surface can be readily engineered through metal nanoparticle decoration, polymer integration, phase modulation, and heterostructure formation, enabling synergistic enhancements in conductivity, catalytic activity, and signal amplification [48, 49]. These properties collectively make MoS_2 an exceptionally effective electrochemical transducer, capable of detecting low-abundance cancer biomarkers with high sensitivity, selectivity, and operational stability [50]. Compared with other candidate electrode materials such as graphene, noble metals, metal oxides, and conducting polymers, MoS_2 offers a unique combination of semiconducting behavior, surface chemistry, and structural anisotropy that is particularly advantageous for electrochemical biosensing. Unlike zero-bandgap graphene, the intrinsic and tunable bandgap of MoS_2 enables stronger modulation of interfacial charge transfer upon biomolecular binding, improving signal discrimination near clinically relevant thresholds. Its layered two-dimensional structure exposes a high density of electroactive edge sites, which serve as efficient catalytic centers and stable anchoring points for biorecognition elements. In addition, MoS_2 exhibits a strong affinity toward nucleic acids and proteins through Van der Waals and sulfur-mediated interactions, often reducing the need for extensive surface functionalization. When integrated into nanohybrid architectures, these properties allow MoS_2 to simultaneously enhance sensitivity, selectivity, and signal stability, positioning it as a versatile alternative to purely conductive or metallic sensing platforms for cancer biomarker detection.

Given the rapidly growing interest in this field, there is a clear need to systematically evaluate the material-level advances that have shaped recent MoS_2 nanohybrid based sensing platforms. This review focuses on the strategic engineering of MoS_2 , including its integration with carbon nanostructures, metal and metal oxide nanomaterials, polymers, metal organic framework (MOFs), semiconductor heterostructures, and surface-charge modulation strategies, to enhance biomarker recognition, electron transport, and signal amplification. By consolidating these developments, this review elucidates the design principles underlying

high-performance MoS_2 nanohybrid biosensors and identifies emerging opportunities for their clinical translation. Furthermore, the summary and prospects section highlights the growing adoption of semiconductor based sensing modalities in disease-specific, threshold-oriented diagnostic applications. Threshold-oriented detection refers to a sensing paradigm in which electrochemical responses are deliberately engineered to reliably discriminate biomarker concentrations around clinically established cut-off values, rather than focusing solely on achieving ultra-low analytical limits of detection. This distinction is critical, as clinical decision-making is typically governed by whether biomarker levels exceed or fall below validated thresholds associated with disease onset, progression, or therapeutic response. By prioritizing threshold sensitivity, electrochemical biosensors can be more effectively aligned with real-world diagnostic workflows, ultimately delivering actionable and clinically meaningful outputs that are directly translatable to clinical practice.

2 MoS_2 integrated nanohybrids-based electrochemical sensors

2.1 MoS_2 with carbon nanostructures

Carbon nanostructures such as graphene oxide (GO), graphitic carbon nitride, carbon nanotubes, etc., have become essential components in electrochemical cancer biosensing due to their exceptional electrical conductivity, high surface area, and versatile functionalization chemistry [51]. When integrated with semiconducting transition metal dichalcogenides like MoS_2 , these materials form synergistic heterostructures that significantly enhance charge-transfer kinetics, provide abundant anchoring sites for biorecognition elements, and improve sensor stability in complex biological media [52]. Their tunable surface chemistry enables precise control over probe loading, antifouling behavior, and interfacial electron transport, the critical factors for detecting low-abundance cancer biomarkers at clinically relevant thresholds. Recent studies have leveraged carbon- MoS_2 hybrids to build vertically aligned architectures, hollow nanostructures, and multidimensional composites that deliver amplified electrochemical responses and improved analytical robustness [53]. Collectively, these advances position carbon nanomaterials as key enablers in next-generation MoS_2 -based electrochemical platforms for early and reliable cancer diagnostics. Recent studies of carbon nanostructure- MoS_2 based cancer biosensors are highlighted below.

MoS₂ with graphene oxide hybrids have been widely engineered across the reported studies, yet they follow two dominant design philosophies, orientation-controlled 2D heterostructures and conductive carbon-supported dispersions, each tailored to different sensing priorities. The first study [54] demonstrates the orientation approach by in situ vertically aligning MoS₂ nanosheets on a GO film that exposes abundant edge sites, enhances hydrophilicity, and accelerates interfacial charge transfer for programmed cell death ligand 1 peptide sensing; this vertical geometry maximizes probe loading and impedance contrast for peptide-based ligand 1 recognition. In contrast, the rGO-modified reduced-MoS₂ multilayer platform [55] follows a conductivity-driven design in which rGO acts as a high-mobility transport network suppressing MoS₂ restacking and improving antibody immobilization, enabling dual-mode electrochemical detection of neuron-specific enolase with heightened signal uniformity. The platinum nanoparticles (PtNPs) incorporated rGO-MoS₂ composite [56] further extends this concept by integrating catalytically active PtNPs into the rGO-MoS₂ scaffold, producing a highly conductive and chemically interactive interface that enhances electrocatalytic current and facilitates stable AFP antibody anchoring. Unlike rGO, which primarily enhances lateral electron mobility and suppresses MoS₂ restacking, GO introduces abundant oxygen functionalities that promote strong adsorption of methylene blue [57], enabling the construction of a self-contained, redox-active sensing interface. The GO-MoS₂ composite preserves the essential features seen in rGO platforms, that is, large electroactive surface area, efficient charge-transfer pathways, and dense bioreceptor anchoring, while adding a unique advantage: integrating an intrinsic redox mediator directly into the hybrid matrix, eliminating the need for secondary nanoparticle amplification. MoS₂ continues to contribute catalytically active edge sites and high affinity for antibody conjugation, while GO stabilizes the dispersion of MoS₂ nanosheets and strengthens dye-surface interactions, supporting a highly stable, label-free readout. This design yields a broad log-linear response for matrix metalloproteinase-7 and an ultralow detection threshold, reaffirming that carbon-MoS₂ hybrids, whether based on reduced or oxidized graphene, can be strategically engineered to modulate interfacial electron transfer, probe density, and signal-transduction mechanisms to meet diverse cancer biomarker detection requirements. Despite differences in target analytes and device architecture, all three systems share a common mechanistic foundation: rGO provides the primary electron-transport backbone and structural dispersion, MoS₂ contributes catalytic edge sites and chemical affinity for biomolecular capture, and additional nanoscale modifications (vertical alignment, minimized restacking, or nanoparticles decoration) tune the

interfacial microenvironment to optimize sensitivity, stability, and cancer-biomarker specificity.

Graphitic carbon nitride-based sensing platforms share a unifying material principle: g-C₃N₄ acts as a metal-free semiconducting scaffold whose nitrogen-rich surface chemistry enables dense bioreceptor immobilization while synergizing with co-integrated nanomaterials to overcome its intrinsic conductivity limitations. In the PSA aptasensor [58], g-C₃N₄ nanosheets were hybridized with MoS₂ quantum dots and gold nanoparticles (AuNPs) to create a hierarchically conductive interface in which AuNPs provide rapid electron shuttling and efficient aptamer attachment, while MoS₂ quantum dots contribute catalytic activity, collectively amplifying the electrochemical recognition of PSA. A similar synergistic strategy underpins the CA125 aptasensor [59], where g-C₃N₄ is coupled with MoS₂ and Fe₃O₄ nanoparticles to form a magnetically responsive, high-surface-area electrode that enhances target capture and facilitates dual-probe voltammetric readout using methylene blue and [Fe(CN)₆]^{3-/4-}. Although differing in analyte and structural design, both systems rely on g-C₃N₄'s role as a chemically active, biocompatible, and stable 2D base layer, while MoS₂ introduces additional electroactive edge sites, and Fe₃O₄/Au nanostructures provide signal amplification pathways. These studies consistently demonstrate that tailoring g-C₃N₄ with complementary nanocomponents unlocks high-density probe loading, accelerated charge-transfer kinetics, and robust discrimination of cancer biomarkers in complex matrices, marking g-C₃N₄ hybrids as versatile and powerful platforms for electrochemical oncology diagnostics.

Extending the theme of engineered carbon-MoS₂ hybrid interfaces, carbon hollow nanorods modified MoS₂ integrated with a DNA hexahedral nano framework [60] exemplifies how carbon materials can be architected not only to improve electron transfer and surface accessibility but also to serve as active structural elements in self-powered signal amplification schemes. In this design, MoS₂ is transformed into hollow, carbon-coated nanorods that are anchored on a 3D carbon cloth substrate, and these are then coupled with DNA nanostructures that provide scaffolded signal amplification through programmed hybridization cascades. Unlike the rGO and GO hybrids discussed earlier, where enhanced conductivity and probe anchor density were the primary material contributions, the carbon coating here plays a multifunctional role by (i) stabilizing the hollow MoS₂ architecture against collapse, (ii) facilitating rapid charge transport through a continuous carbon network, and (iii) improving mechanical contact with the cloth substrate to support self-powered biofuel-cell operation. The DNA hexahedral framework further elevates signal output by organizing multiple redox events per binding interaction, effectively amplifying the electrochemical response without external power. This

hybrid integration yields attomolar-level detection of cancer-associated miRNAs with dual electrochemical readouts, demonstrating that carbon-enriched MoS₂ architectures, whether in the form of rGO sheets, oxidized graphene, or hollow carbon coatings, can be tailored to specific signal-generation schemes, including catalysis, label-free binding, or autonomous energy harvesting, to meet diverse analytical demands in cancer diagnostics.

Another significant example of carbon-enhanced MoS₂ sensing interfaces is the graphitic nano-onion/MoS₂ composite developed for electrochemical detection of DNAs of human papilloma viruses, HPV-16 and HPV-18, biomarkers associated with cervical cancer [61]. In this design, graphitic nano-onions, spherical sp²-carbon structures derived from nanodiamonds, are combined with MoS₂ nanosheets to form a hybrid platform with improved electrical conductivity and electron transfer kinetics compared to MoS₂ alone. The nano-onion component provides a highly conductive, graphitic support that facilitates rapid charge movement and uniform dispersion of the MoS₂ nanosheets, while the layered MoS₂ offers abundant surface edge sites for stable DNA adsorption and hybridization. Through covalent conjugations between functional groups on the nano-onions and amine-modified MoS₂, the composite achieves effective immobilization of target DNA probes, enabling sensitive and selective detection of HPV-derived sequences from cancer cell lines. This material strategy underscores the benefit of introducing 3D carbon nanostructures beyond planar rGO/

GO supports to further amplify interfacial conductivity and analytical responsiveness in cancer-related DNA sensing.

Overall, carbon-MoS₂ nanohybrid platforms consistently demonstrate that integrating conductive carbon architectures, whether GO, rGO, hollow carbon coatings, or graphitic nano-onions, effectively overcomes MoS₂'s intrinsic conductivity limits while expanding its electroactive surface. Across all studies, carbon materials enhance electron transport, stabilize MoS₂ dispersion, and provide abundant functional sites for robust bioreceptor attachment, enabling sensitive detection of diverse cancer biomarkers. Whether through redox-active GO matrices, high-mobility rGO networks, 3D carbon-coated nanorods, or nano-onion supports, these hybrids achieve stronger signal transduction and versatile assay formats. Table 1 compares the electroanalytical performances of various carbon nanostructures integrated with MoS₂ nanohybrids towards cancer biomarker detection. Collectively, they establish carbon-engineered MoS₂ as a powerful material family for next-generation electrochemical cancer diagnostics.

2.2 MoS₂ integrated with noble metal nanomaterials

2.2.1 MoS₂ with gold nanomaterials

MoS₂ has emerged as a versatile platform for label-free and hybrid biosensors owing to its high surface area, abundant active edge sites, and tunable electronic properties. Integration with noble metals, particularly AuNPs, has been widely employed to enhance conductivity, facilitate bioconjugation, and improve electron transport. For instance, a MoS₂ nanosheet-based immunosensor for the detection of thyroid hormone triiodothyronine (T3) was fabricated by sequential electrodeposition of MoS₂ and AuNPs, followed by antibody immobilization [62]. The stepwise fabrication of the proposed immunosensor is displayed in Fig. 2a. Extending this concept, paper-based biosensors incorporating MoS₂/AuNPs were developed for oncogenic microRNAs (miRNA-21 and miRNA-155), demonstrating the feasibility of low-cost, disposable devices for rapid biomolecular sensing [63]. Similarly, cancer antigen 125 (CA-125) detection was achieved using exfoliated MoS₂ sheets decorated with AuNPs, leveraging the layered structure for enhanced immunosensor performance [64], while aptamer-functionalized Au nanoflowers on MoS₂ enabled ovarian cancer marker detection with high biointerface stability [65].

Dual-mode electrochemical and surface-enhanced Raman scattering (SERS) immunosensors have further exploited MoS₂/AuNP nanocomposites. A PSA sensor employed 2D MoS₂ nanosheets decorated with AuNPs on a SPE (Fig. 2b), combining electrochemical and SERS

Table 1 Electrochemical performances of carbon nanostructures integrated MoS₂ hybrids for cancer biomarkers detection

Sensor	Biomarker	Linear range (ng mL ⁻¹)	LOD (ng mL ⁻¹)	Real sample	Ref.
MoS ₂ -GO-ITO	PD-L1	25–500	2	Human serum	54
r-MoS ₂ -rGO	NSE	0.1–100	1	—	55
PtNPs-MoS ₂ -rGO	AFP	1 × 10 ⁻³ – 10 ²	1.2 × 10 ⁻⁵	Human serum	56
MB-MoS ₂ -GO	MMP-7	0.01–75	7 × 10 ⁻³	Human serum	57
MoS ₂ -g-C ₃ N ₄ -CS-AuNPs	PSA	0–250	7.1 × 10 ⁻⁵	Human serum	58
g-C ₃ N ₄ -MoS ₂ -Fe ₃ O ₄	CA125 (labeled)	2–10*	0.202*	Human serum	59
	CA125 (label-free)		0.215*		
MoS ₂ -CC	miRNA-199a	1 × 10 ⁻⁷ – 0.1 [#]	4.9 × 10 ^{-9#}	Human serum	60
MoS ₂ -nano-onion	HPV-16	5 × 10 ⁻³	5 × 10 ⁻³	—	61
	HPV-18	– 5	5 × 10 ⁻³		

AFP, Alpha fetoprotein; CC, Carbon cloth; CS, Chitosan; HPV, Human papilloma virus; ITO, Indium tin oxide; MMP-7, Matrix metalloproteinase-7; MB, Methylene blue; NSE, Neuron-specific enolase; PD-L1, Programmed cell death ligand 1; PSA, Prostate specific antigen; #, nM; *, U mL⁻¹

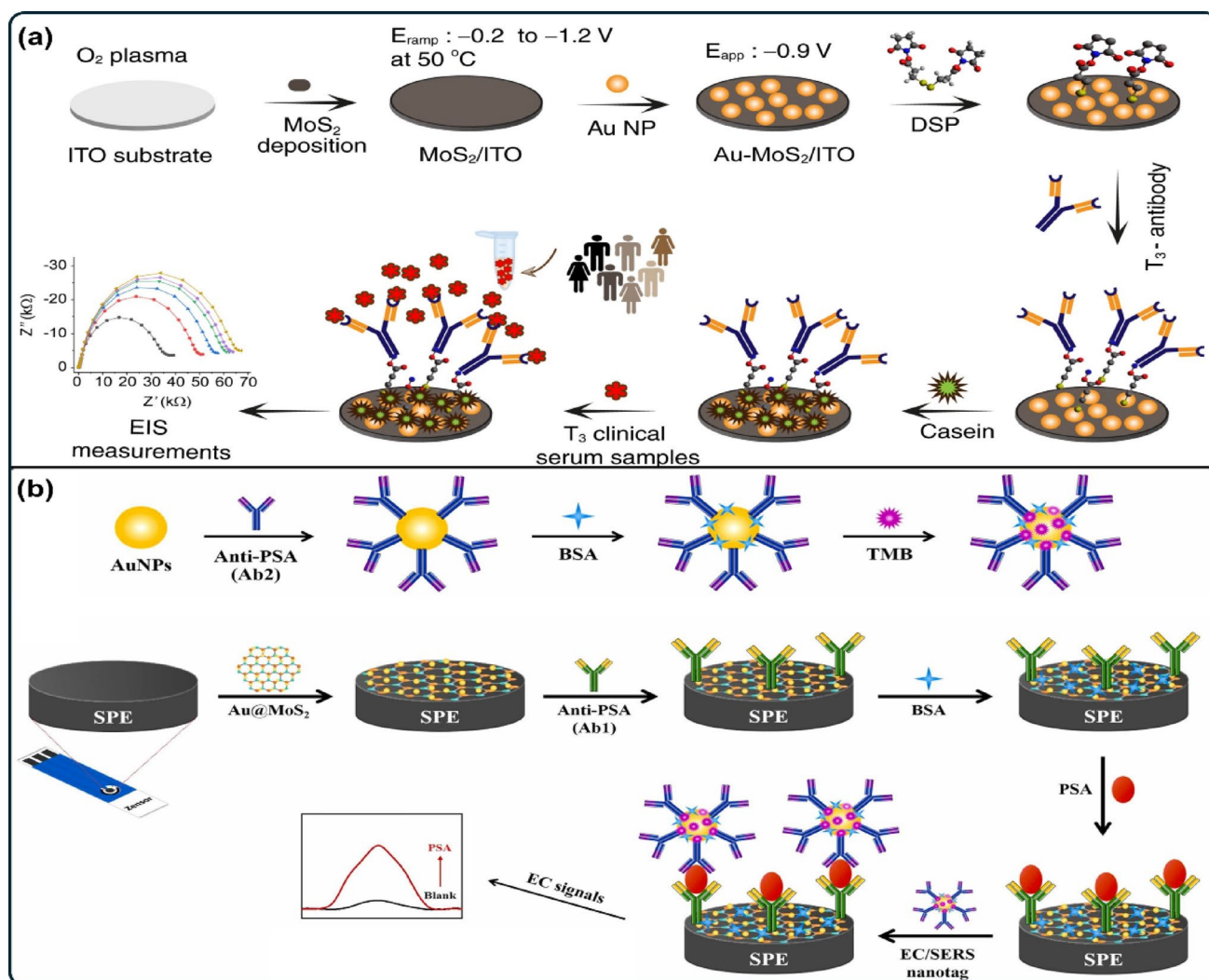


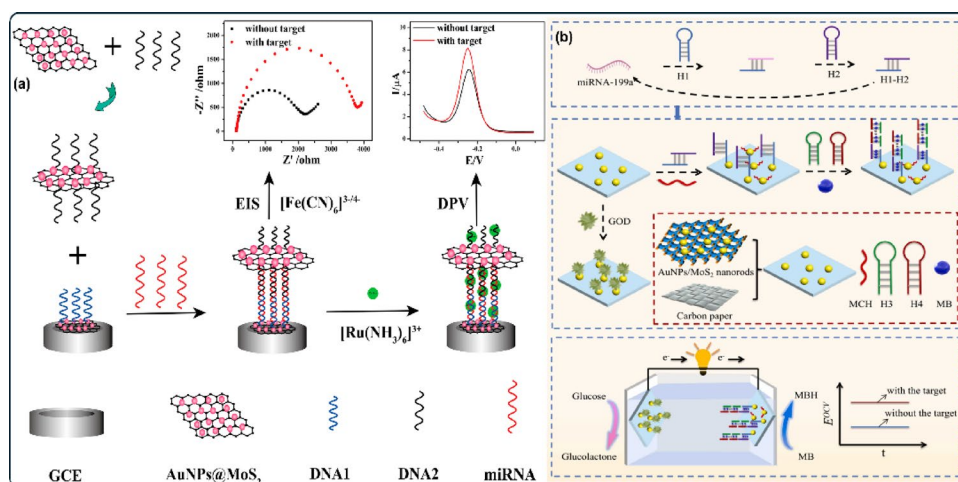
Fig. 2 **a** Graphical representation for the stepwise fabrication of triiodothyronine immunosensor. Reproduced with permission from [62], **b** schematics for the construction of an immunosensor for PSA detection. Reproduced with permission from [66]

readouts via Au nanotags conjugated with secondary antibodies and 3,3',5,5'-tetramethylbenzidine (TMB) [66]. Similarly, the integration of 2D conductors, such as $Ti_3C_2T_x$ MXene, with MoS_2 and in-situ reduced AuNPs enabled highly selective interleukin-6 (IL-6) detection, with MoS_2 providing catalytic activity and scaffold support while the metallic component facilitated rapid electron transport [67].

Flower-like MoS_2 nanostructures decorated with AuNPs have been employed for diverse targets, including human papillomavirus HPV-16 L1 and CA-72-4, where the high surface area and charged morphology enhance antibody attachment and sensor stability [68, 69]. Composites of rGO and MoS_2 with AuNPs have been utilized for miRNA-34a detection on disposable electrodes, integrating conductivity, active site density, and electron-transfer facilitation [70]. Similarly, a dual-mode DNA sandwich sensor for

miRNA-21 employed AuNP-decorated MoS_2 nanosheets, using ferri/ferrocyanide and hexaamineruthenium redox probes to interrogate hybridization [71]. The stepwise fabrication of the sandwich sensor and its representative electrochemical responses are shown in Fig. 3a. In another work, a chronocoulometric platform based on semiconductive 2 H-phase MoS_2 nanosheets with optimized AuNP decoration further illustrates that nanosheet thickness and AuNP spacing critically influence probe density, hybridization efficiency, and selectivity against interfering miRNAs [72]. Finally, a self-powered biofuel cell architecture exploiting MoS_2 as a catalytic anode material has been demonstrated for continuous monitoring of CEA, interfaced with glucose and lactate oxidases to generate bio-current without external power [73]. Stepwise fabrication of the self-powered biofuel cell is displayed in Fig. 3b. Collectively, these studies underscore the versatility of MoS_2 -based materials in

Fig. 3 **a** Schematic representation of dual-mode sandwich-type DNA sensor and electrochemical responses. Reproduced with permission from [71], **b** graphical representation of various steps involved in the fabrication of a self-powered biofuel cell-based biosensor. Reproduced with permission from [73]



electrochemical biosensing, where rational integration with noble metals, 2D conductors, or enzymatic systems enables high-performance, label-free detection across a spectrum of cancer biomarkers. Table 2 summarizes the electroanalytical performances of various AuNPs integrated MoS₂ nanohybrids based biosensors for the detection of cancer biomarkers.

2.2.2 MoS₂ with silver nanoparticles

When decorated with silver nanoparticles (AgNPs), MoS₂ transforms into a highly active transduction platform capable of exceptional biomarker discrimination. Two works have been reported so far to demonstrate the growing role of engineered MoS₂ nanostructures with AgNPs as versatile sensing platforms for cancer diagnostics. The first work integrates functionalized MoS₂ nanosheets with SERS-active Ag nanorods to develop a dual-mode biosensor that detects cancer-related miRNA-106a with enhanced reliability through simultaneous electrochemical and Raman validation [74]. This developed sensor exhibited a low detection limit of 433.34 fM with a linear detection range of 100 fM to 1 nM, reported as a potent, highly sensitive, and reliable tool for early cancer diagnosis. The second employs MoS₂ nanoflowers decorated with PdAgPt trimetallic nanoparticles to construct an electrochemical immunosensor capable of ultrasensitive Pepsinogen I detection for gastric cancer screening [75]. The sensor achieved a linear detection range of 0.5–200 ng mL⁻¹, and a LOD of 0.173 ng mL⁻¹, representing a significant advancement for gastric cancer monitoring. Together, they emphasize how coupling MoS₂ with silver nanostructures significantly boosts sensitivity, signal amplification, and diagnostic robustness, reinforcing MoS₂ composites as promising candidates for next-generation clinical biomarker biosensing.

2.2.3 MoS₂ with platinum nanoparticles

MoS₂ continues to gain prominence as a catalytic and interfacial material in electrochemical biosensing, with recent studies demonstrating its adaptability across diverse electrode architectures and detection strategies. Three studies were reported with PtNPs, where all of them harness the layered structure of MoS₂ nanosheets as foundational sensing platforms, each pairing them with PtNPs modifications for enhanced electrochemical detection of cancer-related biomarkers. The first work demonstrates a distinct Pt-based platform where Pluronic-assisted shear-exfoliated MoS₂ nanosheets improve surface wettability and shift oxidation potentials, enabling selective discrimination of homovanillic acid over uric acid [76]. This work demonstrates that a simple exfoliation and deposition of modified MoS₂ nanosheets on a Pt electrode can enable selective electrochemical detection of homovanillic acid in complex media, such as urine, with a linear range of 50–5000 μM and an LOD of 9.76 μM, offering a potential platform for breast cancer metabolite screening under near-realistic conditions. The second work employs a Pt-tungsten alloy nanocrystal growth on MoS₂ sheets to detect H₂O₂ released from breast-cancer cells, leveraging the hybrid's enhanced catalytic interaction with H₂O₂ [77]. Through in-situ growth of Pt-tungsten (PtW) nanocrystals on MoS₂, the hybrid composite combines the high surface area and layered structure of MoS₂ with the catalytic/electronic properties of the PtW nanocrystals (Fig. 4a). The sensor displayed a linear range of 1–0.2 mM, an LOD of 5 nM, and a sensitivity of 1.71 μA μM⁻¹ cm⁻². The strong electrocatalytic activity of the hybrid, along with improved charge-transfer kinetics compared to bare MoS₂, enables real-time monitoring of reactive oxygen species released from live cancer cells. Similar to the previous report, the third work reports a trimetallic nanoflower, PdAuPt-decorated MoS₂, to achieve highly efficient, enzyme-free detection of H₂O₂ released from cancer

Table 2 Electrochemical performances of AuNPs integrated MoS₂ hybrids for cancer biomarkers detection

Sensor	Biomarker	Linear range (ng mL ⁻¹)	LOD (ng mL ⁻¹)	Real sample	Ref.
AuNP-MoS ₂ /anti-T3	Triiodothyronine	0.01–100	2.5×10^{-3}	Human serum	62
AuNP/MoS ₂	miRNA-21 miRNA-155	–	51.6 [#] 59.6 [#]	–	63
Au-PWE/ MoS ₂ -Ab1/ CA-125/BSA/ AuNFs-GOx- Ab2	CA-125	1×10^{-3} – 50	3.6×10^{-4}	Human serum	64
AuNFs@ MoS ₂ /CA125 aptamer/MCH	CA-125	1×10^{-4} – 500 [*]	1×10^{-4} [*]	Human serum	65
TMB/Ab2/ AuNFs-PSA- Ab1/Au@ MoS ₂ /SPE	PSA	5×10^{-3} – 50	3.5×10^{-3}	Human serum	66
Ti ₃ C ₂ T _x /MoS ₂ / AuNFs	IL-6	5–100	2.9×10^{-3}	Human serum	67
Cit-AuNP/ MoS ₂ /AuE	HPV-16 L1	1×10^{-5} – 10,000	3.8×10^{-10}	Human serum	68
MoS ₂ -AuNFs/ GCE	CA72-4	0.001– 200 [*]	2×10^{-5} [*]	Human urine	69
MoS ₂ E/rGO/ SPE	miRNA-34a	1–1000 [#]	0.066 [#]	Human serum	70
DNA2- AuNFs@MoS ₂ / miRNA-21/ MCH/DNA 1/ AuNFs@MoS ₂ / GCE	miRNA-21	0.01–1 [#]	7.8×10^{-7} [#]	Human serum	71
AuNFs@MoS ₂ / SPGE	miRNA	1×10^{-6} – 0.01 [#]	1×10^{-6} [#]	–	72
HCR/CHA/ AuNFs/MoS ₂ nanorods/CC	miRNA-199a	1×10^{-7} – 0.1 [#]	2.4×10^{-8} [#]	Human serum	73

BSA, Bovine serum albumin; cit, Citrate; GCE, Glassy carbon electrode; GOx, Glucose oxidase; AuE, Gold electrode; AuNFs, Gold nanoflowers; AuNFs, Gold nanoparticles; HPV, Human papilloma virus; IL-6, Interleukin 6; MCH, Mercapto-1-hexanol; PWE, Paper working electrode; PSA, Prostate specific antigen; rGO, Reduced graphene oxide; SPE, Screen printed electrode; TMB, 3,3',5,5'-tetramethylbenzidine; T3, Triiodothyronine; MoS₂E, Molybdenum disulfide composite electrode; SPGE, Screen printed graphite electrode; HCR, Hybridization chain reaction; CHA, Catalytic hairpin assembly; CC, Carbon cloth; #, nM; *, U mL⁻¹

cells [78]. The ternary metallic nanoflowers provided abundant catalytic sites and accelerated charge transfer, while the MoS₂ nanosheet support offered a high-surface-area, layered scaffold for stable nanoflower anchoring. This synergistic architecture enabled rapid and sensitive monitoring of intracellular H₂O₂ dynamics under physiological conditions, allowing real-time evaluation of oxidative stress associated with cancer cell activity (Fig. 4b). The sensor exhibited an

LOD of 0.3 nM at a linear range of 1 to 100 nM, with a sensitivity of $8.365 \text{ nA nM}^{-1} \text{ mm}^{-2}$. Although the study focuses primarily on catalytic performance and live-cell detection, the authors demonstrate a robust and responsive sensing interface capable of capturing biologically relevant H₂O₂ fluctuations without requiring additional labels or enzymatic amplification. Together, these works underscore a common theme: MoS₂ acts as a high-surface-area, chemically stable scaffold, and through functionalization, its electrochemical interface is optimized for biomarker sensing in cancer diagnostics.

2.3 MoS₂ with metal oxides

A sandwich-type electrochemical immunosensor was developed for the ultrasensitive detection of AFP using AuNPs and cuprous oxide decorated MoS₂ nanosheets [79]. In this work, the GCE was deposited with AuNPs and immobilized with primary AFP-antibody to facilitate the AFP binding. On the other hand, Cu₂O intercalated MoS₂ nanosheets were prepared and decorated with AuNPs and secondary antibody to complete the antibody-antigen-antibody sandwich type (Fig. 5a). This sensor effectively quantified the AFP concentrations with a linear range from 0.1 to 50,000 pg mL⁻¹ with a detection limit of 37 fg mL⁻¹. Furthermore, the sensor was validated with spiked concentrations of AFP in human serum samples which showed comparable results with ELISA method. In another study, a portable strip-type sensor was developed for the selective detection of 5-nitroquinoline in biological samples using CeO₂ and ZnCo₂O₄ anchored MoS₂ hybrids [80]. 5-Nitroquinoline is commonly produced by cancerous cells, and it can be found in various biological samples including saliva, urine, and blood serum. Also, high level of 5-nitroquinoline can cause various adverse effects such as neurological effects, gastrointestinal distress, fatigue, and hematological effects and hence, sensitive detection is highly significant in clinical research. Initially, CeO₂, ZnCo₂O₄ and MoS₂ were individually synthesized and ultrasonically mixed to form the proposed hybrid, which was then coated over a SPE to form the desired sensor (Fig. 5b). The sensor exhibited excellent activity towards 5-nitroquinoline over a linear concentration range of 0.01–622.21 μM with a detection limit of 9.5 nM. The prepared hybrid synergistically improved the Ce^{3+/4+} redox properties along with improved active sites in which zinc cobaltite improved electrical conductivity and electron transport and the edge sites present in the MoS₂ boosted the electrochemical activity of the developed sensor. Moreover, the sensor successfully quantified 5-nitroquinoline spiked in human urine, saliva and serum samples with good recovery values.

Fig. 4 **a** Graphical illustration of PtW nanocube decorated MoS₂ nanosheets and its electrochemical sensing mechanism. Inset shows the TEM image of PtW nanocube. Reproduced with permission from [77], **b** scheme for the synthesis of Au-Pd-Pt nanoflower decorated MoS₂ nanosheets and **c** electrochemical detection of hydrogen peroxide released from MCF-7 cells. Reproduced with permission from [78]

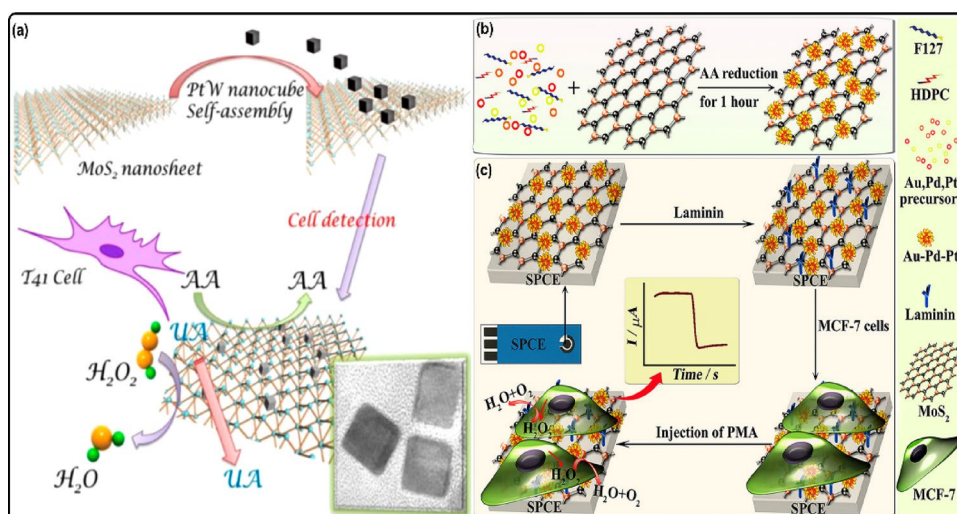
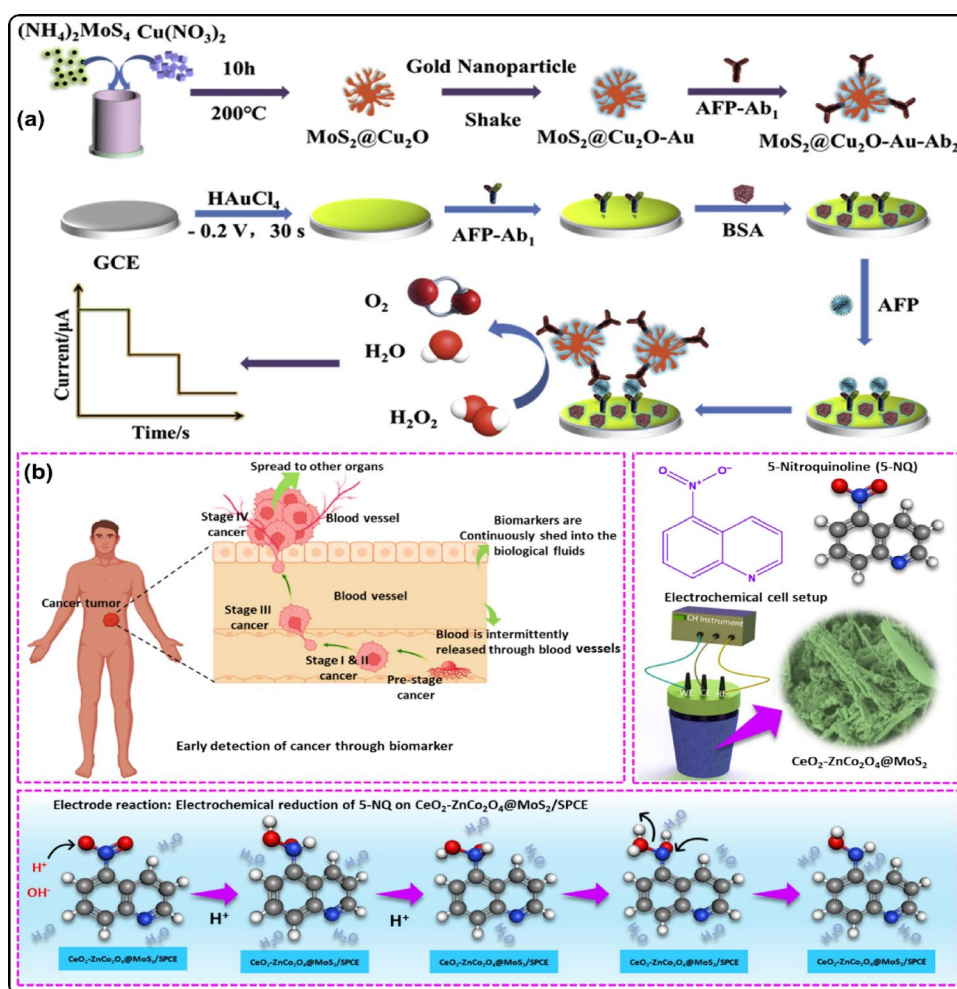


Fig. 5 **a** Graphical illustration of various steps involved in the fabrication of a sandwich-type AFP immunosensor. Reproduced with permission from [79], **b** Graphical representation of cancer progression, electrochemical sensor setup and electrochemical reduction mechanism for 5-nitroquinoline detection at CeO₂-ZnCo₂O₄@MoS₂/SPE sensor. Reproduced with permission from [80]



2.4 MoS₂ with metal organic frameworks

Incorporation of metal organic frameworks (MOFs) into MoS₂ architectures offers a powerful route to merge the high porosity and mass transport advantages of MOFs with the electronic and interfacial strengths of 2D MoS₂. This synergy is exemplified in a tricopper benzene-1,3,5-tricarboxylate (CuBTC) based MOF/MoS₂ composite used for electrochemical immunodetection of the ovarian cancer biomarker CA-125 [81], where the MOF provides abundant binding sites and enhanced diffusion pathways while MoS₂ ensures efficient electron transport, enabling dense antibody loading and stable signal transduction. In contrast, a calcined MOF MIL-68-NH₂ supported MoS₂ nanosheet platform targets H₂O₂, leveraging MoS₂ as a conductive scaffold for dispersing catalytically active MOF domains to achieve rapid, non-enzymatic real-time quantification of H₂O₂ in MCF-7 breast cancer cells [82]. The former sensor achieved a detection range from 0.5 to 500 U mL⁻¹, enabling CA-125 quantification across clinically relevant concentrations, whereas the latter work demonstrated a detection limit down to 6.26 nM for H₂O₂ under optimal conditions. Together, these studies highlight how coupling MoS₂ with porous MOFs or catalytic metals tailors the sensing interface toward either large protein biomarkers or small electroactive molecules, underscoring the versatility of MoS₂ composite engineering in next-generation biosensors.

2.5 MoS₂ with polymers

Polymer-MoS₂ hybrids are rapidly emerging as a powerful class of biointerfaces that combine molecular selectivity with 2D electronic enhancement. Integrating functional polymers with MoS₂ offers a highly tunable route to engineer selective, biocompatible, and electroactive surfaces for cancer-relevant biomarker detection. The first study constructs a peptide-imprinted conductive polymer on a continuous monolayer MoS₂ film, leveraging epitope-level imprinting to create highly selective cavities for matrix metalloproteinase-1 recognition directly on a transferred MoS₂ surface, grown by chemical vapor deposition [83]. This configuration exploits the atomically thin MoS₂ layer to improve charge transport during electropolymerization and enhance binding-induced signal changes in real lung-cancer culture medium. The sensor was found to exhibit an LOD of 1 fg mL⁻¹ at a linear range of 1 to 10 pg mL⁻¹. In the other study, the MIPs were integrated with exfoliated MoS₂ nanosheets, presenting a versatile route for selective electrochemical detection of TMAO, a gut metabolite produced by dietary L-carnitine and choline metabolism [84].

MoS₂ nanosheets provide an enhanced electrochemical interface, and polymer imprints ensure high analyte selectivity, yielding robust detection in aqueous samples. This developed sensor showed an LOD of 1.4 μM at a linear range of 30 to 210 μM with a sensitivity of 1.21 μA μM⁻¹. Together, these studies demonstrate that whether MoS₂ is used as a continuous film or as dispersed nanosheets within an electropolymerized scaffold, its integration with functional polymers markedly improves surface area, electron mobility, and biomolecule-specific interactions, underpinning robust sensing in complex biological media.

2.6 MoS₂ with other materials

A label-free electrochemical biosensor was constructed using few-layer MoS₂ nanosheets obtained via shear-stripping, exploiting the intrinsic affinity difference of MoS₂ toward single-stranded versus double-stranded DNA for highly sensitive detection of circulating tumor DNA (ctDNA) [85]. The sensing mechanism relies on the conformational transition of probe DNA upon hybridization with target ctDNA, which modulates MoS₂ adsorption and is transduced using methylene blue as a redox indicator, enabling amplification-free quantification across extremely low concentration ranges. The sensor exhibited a linear range of 1×10^{-7} to 1×10^{-16} M, with an ultralow LOD of 2.5×10^{-18} M, demonstrating its exceptional analytical sensitivity. Unlike most MoS₂-based cancer sensors that depend on metal nanoparticle decoration, polymer integration, or hybrid composites to boost conductivity and biomolecular loading, this work demonstrates that pristine few-layer MoS₂ alone can deliver exceptional responsiveness and ultra-low detection limits for nucleic-acid biomarkers. Its minimalist architecture without complex surface engineering differentiates it from previous MoS₂ platforms and highlights the potential of intrinsic MoS₂-biomolecule interactions to achieve ultrasensitive ctDNA detection with simplified fabrication and broader applicability. In another study, an electrochemical biosensor was developed using a MoSe₂@1T-MoS₂ Van der Waals heterojunction, engineered to enhance charge transfer and biomolecular recognition for the ultrasensitive detection of the breast-cancer biomarker miRNA-155 [86]. The flower-like MoSe₂ provides a highly porous, electron-rich scaffold, while the metallic 1T-MoS₂ phase contributes superior conductivity and abundant defect sites, together forming a synergistic interface for efficient probe RNA immobilization. This sensor displayed a detection range of 1 fM to 1 nM with a LOD of 0.34 fM. This heterostructure platform enabled femtomolar-level detection across a broad analytical range and successfully differentiated miRNA-155 levels in blood from tumor-bearing and healthy mice, with results consistent with RT-qPCR. Unlike most MoS₂-based

sensors that depend on noble-metal decoration or polymer/MOF integration for signal enhancement, this study leverages intrinsic semiconductor-semiconductor coupling to boost electronic sensitivity, offering a distinct materials-driven route for high-fidelity miRNA biosensing suitable for portable, point-of-care cancer diagnostics.

Similarly, an ultrasensitive electrochemical immunosensor for the lung-cancer biomarker, CYFRA 21–1 was developed using a complex hybrid interface composed of $\text{Si}_3\text{N}_4/\text{MoS}_2$ incorporated with MWCNTs, coupled with core-shell magnetic mesoporous silica nanoparticles decorated with AuNPs as a signal-amplifying label [87]. The composite provided a highly conductive, high-surface-area scaffold for stable antibody immobilization, while the magnetic AuNPs enhance immunocomplex formation and boost electrochemical response. The platform demonstrated ultrasensitive detection of CYFRA 21–1 with a low detection limit (2 fg mL^{-1}) and a broad linear range (0.01 to 1 pg mL^{-1}). This integrated strategy enables highly efficient antigen recognition and robust signal amplification, offering a promising route for early-stage lung cancer diagnostics. In a recent study, a self-powered electrochemical biosensor based on a MnS and MoS_2 composite electrode was developed, which leverages cascade amplification (catalytic hairpin assembly + hybridization chain reaction) for ultrasensitive detection of cancer-related miRNA biomarkers [88]. The composite electrode enhances enzyme loading and accelerates electron transfer, thus enabling efficient signal generation without an external power supply. Upon the presence of target miRNA-199a, cascade reactions trigger strong signal amplification, producing a clear current output. The device demonstrated a linear range of 0.5 fM to 100 pM , with a LOD of 0.14 fM , underscoring its high analytical activity. Moreover, the system's readout is transmitted via Bluetooth to a smartphone interface, demonstrating potential for portable, real-time, point-of-care diagnostics. This work combines self-powered operation and molecular-level signal amplification, with MoS_2 -based material engineering, offering a powerful paradigm for miRNA detection in cancer diagnostics, particularly attractive for decentralized screening and monitoring applications.

3 Challenges and outlook

3.1 Anti-fouling strategies for MoS_2 -based electrochemical sensors

A major challenge for translating MoS_2 -based electrochemical biosensors from laboratory studies to clinical applications is biofouling caused by nonspecific adsorption of proteins, lipids, and other components present in complex biological

fluids such as serum, plasma, and saliva. Such nonspecific interactions can block electroactive sites, alter interfacial charge transfer, and lead to signal drift or loss of sensitivity, particularly during prolonged operation [89, 90]. Owing to its high surface energy and strong affinity for biomolecules, pristine MoS_2 is especially susceptible to surface fouling in real samples, necessitating deliberate interface engineering for stable performance. Several antifouling strategies have therefore been explored to mitigate nonspecific adsorption while preserving biomolecular recognition. Surface passivation using hydrophilic or zwitterionic polymers, polyethylene glycol coatings, and protein-blocking layers such as bovine serum albumin has been widely employed to create hydration barriers that resist non-specific protein attachment [91, 92]. Biomimetic coatings and molecularly imprinted surfaces further improve selectivity by providing steric and chemical discrimination at the sensing surface [93]. In parallel, nanohybrid design plays a crucial role in anti-fouling behavior, such as integrating MoS_2 with carbon nanostructures, conducting polymers, or porous frameworks, which can reduce nanosheet restacking, shield basal planes, and generate sterically hindered architectures that suppress nonspecific binding. Collectively, these anti-fouling approaches are essential for maintaining signal fidelity, reproducibility, and long-term stability of MoS_2 -based electrochemical sensors on real biofluids and represent a key design consideration for clinically translatable cancer diagnostics.

3.2 Reproducibility and phase stability of 1T- MoS_2 hybrids

The metallic 1T phase of MoS_2 is frequently highlighted in electrochemical biosensing due to its superior electrical conductivity, high density of defect sites, and enhanced charge-transfer kinetics compared to the semiconducting 2H phase. However, despite these advantages, the 1T phase is intrinsically metastable and prone to gradual reversion to the thermodynamically favored 2H phase under ambient conditions, electrochemical cycling, or prolonged exposure to aqueous and biological environments [94]. This phase instability introduces variability in electronic properties and sensor performance, raising concerns regarding reproducibility and long-term operational reliability. From a translational perspective, the synthesis of phase-pure or phase-controlled 1T- MoS_2 remains challenging, as commonly used chemical exfoliation and lithium intercalation routes often yield mixed 1T/2H phases with batch-to-batch variability [95]. While strategies such as heteroatom doping, interfacial strain engineering, hybridization with conductive supports, and encapsulation with nanocomposites have been reported to partially stabilize the 1T-phase, systematic studies evaluating phase retention during storage and repeated

sensing cycles remain limited [96]. Consequently, although 1T-MoS₂ hybrids offer clear short-term sensitivity advantages, their practical deployment in clinical biosensors will require improved phase stabilization strategies, standardized characterization protocols, and explicit reporting of phase composition over time. A critical balance between electronic performance and structural stability is therefore essential when selecting 1T-MoS₂ architectures for clinically relevant electrochemical sensing platforms.

3.3 Scalability and cost-benefit considerations for point-of-care deployment

From a manufacturing perspective, the scalability of MoS₂-based electrochemical biosensors must be evaluated not only in terms of fabrication reproducibility but also relative cost-performance advantages over established graphene-only platforms. While graphene electrodes benefit from mature large-area production routes such as chemical vapor deposition and ink-based printing, MoS₂ offers complementary advantages that justify its integration despite added material complexity. In particular, MoS₂ provides an intrinsic semiconducting bandgap, high edge-site density, and strong affinity for biomolecular probes, enabling higher signal modulation per binding event and improved selectivity without excessive surface functionalization [97, 98]. Cost-benefit considerations suggest that MoS₂-based hybrids may reduce overall device complexity by minimizing the need for additional signal amplifiers or redox labels commonly required in graphene-only sensors. Furthermore, solution-processable MoS₂ nanomaterials, compatible with drop-casting, screen-printing, and flexible substrates, support low-cost fabrication routes suitable for disposable point-of-care devices. However, achieving consistent exfoliation yield, phase composition, and long-term material stability remains a bottleneck that must be addressed before MoS₂ sensors can fully match the manufacturing maturity of graphene [99]. Thus, MoS₂-based platforms are best positioned as performance-enhancing alternatives rather than direct replacements, particularly in applications where sensitivity, threshold discrimination, and biointerface control outweigh marginal increases in material processing cost. In addition, the shelf-life of MoS₂-modified electrodes represents a critical challenge, as oxidation, nanosheet restacking, and surface contamination during storage can degrade sensitivity over time. Studies have shown that chemically exfoliated MoS₂ undergoes progressive oxidation deterioration without protective layers, leading to changes in structure and performance [100]. Furthermore, atomically thin MoS₂ is prone to oxidative attack at defects and edge sites, which can degrade its electronic and surface properties [101]. Strategies including surface passivation, encapsulation, and

integration with stabilizing matrices such as polymers or carbon nanostructures have shown promise in improving environmental stability and preserving sensing performance [102]. Addressing these manufacturability and shelf-life challenges will be essential for advancing MoS₂ nanohybrid sensors from laboratory demonstrations to clinically viable point-of-care diagnostic platforms.

3.4 Standardization and fabrication challenges

A critical yet under-addressed challenge in MoS₂-based electrochemical biosensors is the lack of standardized fabrication protocols, particularly regarding exfoliation yield and nanosheet quality. Variations in exfoliation methods, such as liquid-phase exfoliation, shear mixing, sonication, or chemical intercalation, often produce MoS₂ with inconsistent layer numbers, lateral dimensions, defect densities, and phase compositions. These variations directly influence charge-transfer kinetics, biomolecular adsorption, and ultimately the sensor's limit of detection and reproducibility [103, 104]. At present, many studies report analytical performance without clearly defining exfoliation yield, nanosheet thickness distribution, or batch-to-batch variability, making cross-study comparison difficult. Establishing standardized reporting metrics such as average layer number, edge-to-basal plane ratio, phase fraction (1T/2H), and mass-normalized electroactive surface area would significantly improve reproducibility and benchmarking across platforms. Future progress toward clinically deployable MoS₂ sensors will require not only optimized material synthesis but also community-wide agreement on fabrication and characterization standards to ensure reliable performance translation from laboratory studies to scalable diagnostic devices.

4 Summary and prospects

Cancer diagnosis continues to face fundamental challenges in achieving early, accurate, and minimally invasive detection, particularly for biomarkers present at trace concentrations during initial disease stages. While conventional imaging and laboratory techniques remain indispensable, their limitations in sensitivity, accessibility, and suitability for continuous monitoring underscore the need for alternative diagnostic strategies. Biomarker-based approaches, especially those leveraging electrochemical biosensing, offer an effective pathway to address these unmet clinical demands by enabling rapid, low-volume, and point-of-care compatible detection platforms. Electrochemical biosensing is rapidly becoming a crucial tool for cancer diagnosis, owing to its efficient signal-to-electron conversion and suitability for low-volume, point-of-care testing. Its most

significant potential, however, lies in combining these sensing techniques with semiconductor-engineered interfaces that can convert biological recognition into measurable electrical signals. Within this diagnostic framework, semiconducting electrode materials play a decisive role in converting subtle biomolecular interactions into measurable signals with clinical relevance. Among emerging candidates, MoS₂ has established itself as a highly adaptable sensing platform due to its layered two-dimensional structure, tunable electronic properties, and strong affinity for biological recognition elements. These characteristics allow for precise regulation of charge transport at the interface. Consequently, MoS₂-based electrodes are highly sensitive to the subtle physicochemical changes caused by rare cancer biomarkers, effectively connecting biological detection events with meaningful electrochemical signals. The studies discussed in this review demonstrate that both pristine and hybrid MoS₂ architectures integrated with carbon nanostructures, metal nanoparticles, metal oxides, polymers, MOFs and other nanomaterials can substantially enhance charge transfer, signal stability, and biomarker accessibility, thereby enabling detection across clinically meaningful concentration regimes.

Looking forward, the translation of MoS₂-based electrochemical sensors into practical cancer diagnostics will depend on moving beyond proof-of-concept sensitivity toward threshold-oriented detection, where sensor responses are designed to reliably discriminate biomarker concentrations across clinically defined cut-off values [105–107]. For example, serum PSA levels are commonly interpreted using a threshold of approximately 4 ng mL⁻¹ for prostate cancer screening, with age-specific lower cut-off values often recommended for younger individuals to improve early detection. Similarly, the ovarian cancer biomarker CA-125 is generally considered elevated above 35 U mL⁻¹, and CA 19 – 9 used in pancreatic cancer monitoring, typically employs a clinical cut-off value of approximately 37 U mL⁻¹. In addition, reference intervals for CEA are generally < 2.5 ng mL⁻¹ in nonsmokers and < 5 ng mL⁻¹ in smokers, reflecting commonly applied clinical thresholds for colorectal and other cancers [108]. These clinically defined cut-off values exemplify how threshold-oriented detection aligns analytical outputs with actionable diagnostic decision points in clinical practice. Achieving this will require tighter control over semiconductor interfaces, antifouling strategies for complex biofluids, and systematic validation using real patient samples. Simultaneously, miniaturization and multiplexing will advance through 2D semiconductor device designs such as vertically stacked Van der Waals heterostructures, dual-gate field-effect sensors, nanoelectrode arrays, and flexible microfluidic platforms for continuous monitoring. Integrating MoS₂-based sensors into digital

health systems via on-chip calibration, machine-learning-based signal analysis, and wireless data collection will support personalized cancer monitoring outside traditional hospital environments.

Ultimately, the integration of semiconductor physics, nanoscale material engineering, and electrochemical instrumentation establishes MoS₂ and its hybrids as key components for future cancer diagnostics. Enhancing threshold-aware device design, boosting clinical robustness, and exploiting the tunability of 2D semiconductors allow electrochemical biosensors to move from lab prototypes to real-world diagnostic tools. This transition can facilitate earlier detection, support adaptive therapy choices, and enable long-term disease monitoring.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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