Molybdenum Disulfide Biosensor for Cancer Biomarker Detection

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Molybdenum disulfide (MoS_2) is a promising two-dimensional (2D) nanomaterial, whose unique adjustable bandgap shows excellent electronic and optical properties in the construction of biosensor interfaces. It not only has the advantages of a high catalytic activity and low manufacturing costs, but it can also further expand the application of hybrid structures through different functionalization, and it is widely used in various biosensors fields.

Keywords: molybdenum disulfide ; electrochemical sensor ; optical sensor ; cancer biomarkers ; detection

1. Introduction

Cancer is the world's leading cause of death and the second most common disease [1]. At present, more than 200 types of cancers have been found. In general, imaging technologies such as ultrasound, positron emission tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT) are used for early screening, followed by confirmation through tissue biopsy and histology, so that patients can be treated in a timely manner, which can dramatically reduce cancer mortality [2][3][4]. However, traditional cancer detection methods are often invasive, expensive, complex, and time consuming. Rapid diagnosis and early prevention are crucial for the clinical treatment and management of cancer [5]. Cancer biomarkers, as important components of detection, prognosis, and providing an etiological analysis of cancer, are abnormal quantities of biological molecules generated by the body's response to the disease or directly by the cancer tumor itself, including DNA, RNA, genes, proteins, enzymes, peptides, exosomes, and metabolomics [6]. So far, the main cancer biomarkers that have been discovered include carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), carbohydrate antigen 15-3 (CA15-3), human epidermal growth factor receptor 2 (HER2), vascular endothelial growth factor 165 ($VEGF_{165}$), tissue-specific antigen (TPS), prostate-specific antigen (PSA), alpha-fetoprotein (AFP), squamous cell carcinoma antigen (SCCA), circulating tumour cells (CTCs), microRNAs, and exosomes [7]. They typically exist in the blood, urine, tears, oral fluids, and other tissues [8]. Cancer biomarker detection has accelerated the process of cancer diagnosis, and can obtain higher sensitivity and faster cancer screening. Enzyme-linked immunosorbent assay (ELISA) [9], polymerase chain reaction (PCR) [10], clustered regularly interspaced short palindromic repeats Cas9 (CRISPR-Cas9) [11], loop-mediated isothermal amplification (LAMP), time-resolved fluorescence spectroscopy (TR-FS), radioimmunoassay (RIA), and electrophoresis [12] have been used for the detection of cancer biomarkers [13]. In addition, emerging technologies such as artificial intelligence, long read sequencing, microarrays, DNA methylation, and liquid biopsy are also committed to the development and high throughput profiling of many biomarkers to strengthen cancer management and improve early screening [14][15].

In recent years, compared with traditional technologies, biosensors have potential advantages such as a high sensitivity and selectivity, high accuracy, low cost, fast detection, high stability, availability, and ease of operation. They play an important role in diagnosing and quantitatively analysing biomarker concentrations, and are widely used in various fields such as healthcare, food inspection, and environmental testing [16]. Biosensors use various biomolecules as biometric recognition components, which are fixed on the sensor surface and converted into measurable electronic or optical signals through biological responses with the detection target substance for cancer biomarker detection [17]. Biosensors can be divided into electrochemical, optical, mass-dependent, and radiation sensitive biosensing platforms based on different transduction principles [18][19]. Developing efficient and practical biosensors usually requires consideration of the following aspects: (1) synthesis, manufacture, and assembly of suitable sensing materials; (2) selecting appropriate recognition or capture molecules; and the (3) integration of sensor surfaces with biomolecules [20][21]. With the development of nanotechnology in medicine and biotechnology, more and more researchers are combining different types of nanomaterials with optical, electrical, mechanical, and magnetic sensors to design nanosensors for the detection of cancer biomarkers [22]. Nanobiosensors are generally composed of nanomaterials and a sensor based on biometric

recognition elements [23]. They can be combined according to the interaction of the affinity bond, covalent bond, cross-linking, capture, and physical adsorption [24].

Among the various nanomaterials, 2D-layered nanomaterials have attracted widespread research interest due to their quantum confinement, high absorption coefficient, high specific surface area, and tunable bandgap characteristics [25]. Among them, graphene has excellent physical properties, chemical adjustability, and application potential, and its synthesis, properties, and applications are widely known [26]. The impressive performance of graphene in various fields has aroused strong interest in the exploration of a wider range of 2D-layered nanomaterials “beyond graphene” [27]. Transition metal dichalcogenides (TMDs), as a new class of stable inorganic graphene analogues, have been further studied. Among them, MoS_2 is regarded as a representative of TMDs. Its single molecular layer is composed of an atomic layer of transition metal Mo sandwiched between two sulfur elements S [28]. Mo atoms and S atoms are closely connected by forming a strong covalent bond through coordination, and the interlayer is connected by a weak van der Waals force. This weak connection mode between layers provides conditions for MoS_2 stripping to form a single-layer 2D planar structure [29], showing unique electronic, optical, mechanical, and chemical properties [30][31][32]. Most importantly, due to the confinement of electrons/holes in ultra-thin planar structures, MoS_2 is highly sensitive to changes in the microenvironment [33], thus exhibiting advantages in the construction of biosensing interfaces [34][35].

2. Electrochemical Biosensors for Cancer Biomarkers Detection Based on MoS_2

Electrochemical sensors are mainly composed of sensitive components, signal transduction components, and nano modified electrode structures. Electrochemical analysis technology is an important detection method in the field of biomedicine. Its basic principle is to analyse the changes in current or impedance signals generated by the interaction between the analyte and the electrode surface. It can monitor the charge movement between reaction interfaces and has significant advantages through its fast response [36]. In recent years, sensitive electrochemical biosensors have been developed for the detection of cancer biomarkers [37]. MoS_2 has a hexagonal lattice layered structure, which gives it excellent properties such as a high specific surface area, high electron mobility, thermal stability, catalytic activity, and diamagnetism, which is commonly used in semiconductor materials, catalysts, and lubricating materials, etc. [38][39][40]. The unique adjustable bandgap characteristic of MoS_2 provides excellent photoluminescence properties, which are widely used in optical devices such as photodetectors. Additionally, MoS_2, as a promising emerging nanomaterial, has low manufacturing costs, rich nanostructures, and is easy to functionalize, making it form hybrid structures with other precious metal nanomaterials, which is widely used in the field of electrochemical sensing [41]. This chapter divides electrochemical biosensors into potentiometry, amperometry, impedimetry, and photoelectrochemical (PEC) biosensors according to different signal transductions, and introduces the latest application progress of MoS_2 in cancer biomarker detection.

2.1. Potentiometry

Potentiometric sensors obtain information about analytes by measuring the current when potential changes, mainly including chronoamperometry (CA), cyclic voltammetry (CV), differential pulse voltammetry (DPV), and square wave voltammetry (SWV), which are widely used electrochemical analysis methods. These methods fix the biometric elements (such as antibodies, enzymes and aptamers) on the electrode surface, and monitor the current changes triggered when the analyte combines with the biometric element when the potential between the working electrode and the reference electrode remains constant. Within the linear potential range, the monitored peak current value is directly related to the concentration of the target analyte in the solution, so as to realize the detection of the target.

The electronic properties of MoS_2 are highly dependent on its phase structure. The ultra-thin MoS_2 has a good performance, but it is difficult to maintain stability in an independent state and is easy to aggregate [42]. In order to improve this problem, Ying et al. [43] used liquid-phase exfoliation and surface modification to synthesize 2H-MoS_2, and used platinum nanowire (Pt NWs) arrays as nanopillars, which were added to the ultra-thin 2D MoS_2 interlayer to form Pt NWs arrays@MoS_2 nano hybrid, which improved the specific surface area and porosity, and could be used as “electronic wires” to catalyze electron transfer at the interface, avoiding folding by creating new dimensions. Thus, stability and current signal enhancement were achieved.

Two main reasons that limit the practical application of MoS_2 in electrochemical sensing are that the strong van der Waals force effect between layers, which leads to aggregation and relatively low conductivity in layers [44]. In order to overcome these shortcomings, Su et al. [45] synthesized ionic liquid (IL) functionalized AuNPs/MoS_2/rGO nanocomposites for sensitive detection of cancer-specific target nucleolin. The linear range of the unlabeled electrochemical sensor obtained was 0.5 nM–1.0 μM, and the detection limit was 0.16 nM. Graphene has a large π electronic structure and edge, because

of the synergistic effect, and the combination of MoS_2 and graphene can significantly improve the conductivity and large surface area of MoS_2 [46]. In addition, the introduction of AuNPs into nanocomposites can not only fix the thioaptamer through the Au-S bond, which improves the affinity and specificity, but it can also enhance electron transfer and amplify the electrochemical signal.

2.2. Amperometry

Amperometric sensors achieve quantitative detection of analytes by applying a constant voltage to the sensing platform to detect the current generated by the conversion of corresponding electroactive substances. Because of their convenience and high accuracy, they are widely used in the detection of cancer biomarkers. As a result of the excellent catalytic activity of MoS_2 for the reduction in H_2O_2, Ma et al. [47] used the hydrothermal method to combine MoS_2 nanoflowers (MoS_2 NFs) with p-type metal semiconductor oxide cuprous oxide (MoS_2@Cu_2O), and, at the same time, the introduction of AuNPs generated MoS_2@Cu_2O-Au complexes by Au-S bonds as nanoprobes for signal amplification. The constructed sandwich immunosensor could detect the cancer marker alpha fetoprotein (AFP) of primary liver cancer in the wide linear range of 0.1 pg/mL to 50 ng/mL, demonstrating good application prospects. Ma et al. [48] prepared a sandwich-type electrochemical immunosensor for the sensitive detection of CEA by coupling tri-metallic yolk−shell Au@AgPt nanocubes (Au@AgPt YNCs) loaded on amino-functionalized MoS_2 NFs (MoS_2 NFs/Au@AgPt YNCs) with secondary antibodies. As a result of the biphasic synergistic catalysis, the synthesized MoS_2 NFs/Au@AgPt YNCs as a signal label effectively catalyzed the reduction of H_2O_2 to amplify the current signal, and realized the high-precision detection of CEA in the range of 10 fg/mL–100 ng/mL, with an LOD as low as 3.09 fg/mL (S/N = 3). These works provide ideas for the composite modification of MoS_2 with different nano forms and further applications in biosensing platforms.

2.3. Impedimetry

Impedance sensors are an important type of electrochemical sensing that obtains information about analytes by measuring the conductance through interface reactions on the electrode surface. This type of sensor is very sensitive to the change in electrode, and is in an advantageous position in the detection of biomarkers. Therefore, it is also widely introduced into the construction of the electrochemical sensing platform for the detection of cancer biomarkers. Jia et al. [49] prepared a novel nanohybrid of polyoxometalate-derived MoS_2 nanosheets (pd-MoS_2 NSs) using a hydrothermal method, which exhibited an excellent electrochemical activity and abundant catalytic sites. Furthermore, pd-MoS_2 NSs were vertically grown over β-FeOOH NRs (pd-MoS_2@β-FeOOH), serving as complementary DNA platforms for fixing oncogenes and tumour suppressor miRNA-21, using electrochemical impedance spectroscopy (EIS) to detect miRNA-21, with an LOD as low as 0.11 fM. In addition, microfluidic electrochemical immunochips have been evaluated as a powerful detection platform because of their high sensitivity, low cost, portability, and easy miniaturization. Sri et al. [50] synthesized MoS_2 NFs using the same method, and electrophoretically deposited them on an indium tin oxide (ITO)-coated glass substrate. Because of the morphology of MoS_2 NFs, antibodies can be effectively fixed on the electrode surface through physical adsorption. The biosensor can sensitively detect tumour necrosis factor-α (TNF-α) between 1–200 pg/mL, with an LOD as low as 0.202 pg/mL. Hu et al. [51] first prepared MoS_2 by liquid-phase exfoliation and formed a hybrid film with PDDA, designed a three-electrode system in the microfluidic chip, and introduced a MoS_2/PDDA film modified with anti-AFP as the working electrode, Ag/AgCl as the reference electrode, and ITO as the counter electrode. The linear range of AFP detected by EIS was 0.1 ng/mL to 10 ng/mL, with an LOD of 0.033 ng/mL.

2.4. Photoelectrochemistry (PEC)

PEC utilizes photosensitive materials at the electrode interface as signal converters to analyse the electrical signals generated by analytes under light irradiation, combining the advantages of spectral analysis and electrochemical technology. MoS_2 exhibits excellent characteristics of a tunable bandgap in its transition from a blocky structure to a layered structure. The quantum confinement effect led to good visible light absorption and photoelectric conversion efficiency of layered MoS_2 as a direct bandgap semiconductor under visible light excitation, resulting in photocurrent generation. Therefore, it has been introduced into the application of photoelectrochemical sensing platforms. Hu et al. [52] utilized this mechanism to design a PEC sensing platform based on MoS_2/Au/GaN for the high sensitivity detection of AFP. MoS_2 can suppress the charge transfer of Au/GaN photoelectrodes, leading to a significant decrease in photocurrent. However, the presence of AFP can reduce the inhibitory effect on the photocurrent, thereby utilizing the difference in photocurrent to detect AFP. AFP detection is achieved in a wide linear range of 1.0–150 ng/mL, with an LOD of 0.3 ng/mL. This method has a good sensitivity and high selectivity for AFP detection. Wei et al. [53] synthesized a light-responsive ZnS/C/MoS_2 nanocomposite to construct a PEC immunosensor for detecting CEA, with a linear range of 2.0 pg/mL–10.0 ng/mL and an LOD of 1.30 pg/mL (S/N = 3), showing good analytical characteristics. In addition to the above sensing methods, other sensing methods based on MoS_2 are listed in **Table 1** to detect various cancer biomarkers.

Table 1. Electrochemical biosensors for cancer biomarkers detection based on MoS_2.

Method	Analytes	Electrode/Label	Linear Range	LOD	Ref.
Chronoamperometry	AMACR	Pt NWs array@2H-MoS_2/SPE	0.70–12.50 ng/μL	0.5 pg/μL	[43]
CV	CEA	Ab/rGO/MoS_2@PANI/GCE	0.001–80 ng/mL	0.3 pg/mL	[54]
CV	PSA	Ab/ce-MoS_2/AgNR/SPE	0.1–1000 ng/mL	0.051 ng/mL	[55]
DPV	CEA	Ab/MoS_2-PBNCs/GCE	0.005–10 ng/mL	0.54 pg/mL	[56]
DPV	CEA	Ag/MoS_2@Fe_3O_4-Ab2/CEA/Ab1/Ag/MGCE	0.0001–20 ng/mL	0.03 pg/mL	[57]
DPV	miRNA-182	ssRNA/MoS_2/Ti_3C_2/GCE	1 fM–0.1 nM	0.43 fM	[58]
DPV	CEA	MoS_2-AuNPs/HRP-Ab2/CEA/Ab1/MoS_2-AuNPs/GCE	10 fg/mL–1 ng/mL	1.2 fg/mL	[59]
DPV	Nucleolin	TNA/AuNPs/MoS_2/rGO/GCE	0.5 nM–1.0 μM	0.16 nM	[45]
DPV	CEA	Ab/Pd@Pt/MoS_2-Gr/GCE	0.00001–100 ng/mL	0.005 pg/mL	[60]
DPV	CA125	Ab/CuBTC@MoS_2-AuNPs/SPE	0.5 mU/mL–500 U/mL	0.5 mU/mL	[61]
DPV	anti-retroviral agent indinavir	ZnO NRs/MoS_2 NSs/SPE	0.01–0.66 μM & 0.66–7.88 μM	0.007 μM	[62]
SWV	CEA	CeO2-MoS_2-Pb^{2+}-Ab2/CEA/Ab1/AuNPs/GCE	0.001–80 ng/mL	0.3 pg/mL	[63]
Amperometry	CEA	Ab/Ag/MoS_2/rGO/GCE	0.01 pg/mL–100 ng/mL	1.6 fg/mL	[64]
Amperometry	HBeAg	Au@Pd/MoS_2@MWCNTs-Ab2/HBeAg/Ab1/p-GO@Au/GCE	0.1–500 pg/mL	26 fg/mL	[65]
Amperometry	AFP	MoS_2@Cu_2O-Au-Ab2/AFP/Ab1/AuNPs/GCE	0.1 pg/mL–50 ng/mL	0.037 pg/mL	[47]
Amperometry	AFP	Ab/Pt NDs/PDDA/MoS_2@PPy NTs/GCE	50 fg/mL–50 ng/mL	17 fg/mL	[66]
Amperometry	CEA	MoS_2 NFs/Au@AgPt YNCs -Ab2/CEA/Ab1/AuTNPs/GCE	10 fg/mL–100 ng/mL	3.09 fg/mL	[48]
EIS	CML	pDNA/PANI-MoS_2/ITO	10^{-17}–10^{-6} M	3×10^{-18} M	[67]
EIS	AFP	Ab/MoS_2/PDDA/Ag/AgCl wire	0.1–10 ng/mL	0.033 ng/mL	[51]
EIS	miRNA-21	cDNA/pd-MoS_2@β-FeOOH/Au	1 fM–5 nM	0.11 fM	[49]
EIS	TNF-α	MoS_2 NFs	0.01–200 pg/ml	0.202 pg/ml	[50]
PEC	CEA	ALP-Au-Ab2/CEA /Ab1/ZnS/C/MoS_2/GCE	2.0 pg/mL–10.0 ng/mL	1.30 pg/mL	[53]
PEC	SCCA	Ab/AuNPs/C/MoS_2/GCE	0.005–8 ng/mL	1.8 pg/mL	[68]
PEC	AFP	DNA/Au/GaN	1.0–150 ng/mL	0.3 ng/mL	[52]
PEC	MCF-7 cells	PM6:Y6/anti-EpCAM-MNs /Au NPs/Au-aptamer	10–10,000 cell/mL	9 cell/mL	[69]

3. Optical Biosensors for Cancer Biomarker Detection Based on MoS_2

Optical biosensors bring additional advantages in the fields of biotechnology, environmental research, disease diagnosis, and medical applications due to their high selectivity, and fast and sensitive measurement. The working principle and key performance indicators of optical biosensors largely depend on optical transducers tightly integrated with biological sensing components [70]. Based on different biosensor elements, optical biosensors are divided into colorimetry, electrochemiluminescence (ECL), fluorescence, surface enhanced Raman scattering (SERS), surface plasmon resonance (SPR), and other sensing methods. In combination with MoS_2, the latest application progress in cancer biomarker detection is introduced.

3.1. Colorimetry

MoS_2, with its large surface area and exposed reaction sites, can be used as a nano enzyme to show the catalytic activity and excellent stability of peroxidase, and it simulates natural enzymes to make the substrate colour change. This feature is used to build a colorimetric sensor to detect cancer biomarkers [71][72]. Zhao et al. [73] introduced an aptamer to enhance the catalytic activity of MoS_2 NSs on peroxidase substrates and designed a colorimetric sensor for the intuitive detection of CEA, achieving sensitivity detection of CEA by successfully recording absorbance. The sensor exhibited a linear response in the range of 50 to 1000 ng/mL, with an LOD of 50 ng/mL, demonstrating good specificity and practical application capabilities. Shao et al. [74] utilized the high catalytic activity of MoS_2-AuNPs nanohybrids to reduce $NaBH_4$ to 4-NP and make the yellow solution colourless, and constructed a colorimetric immunosensor for CEA detection. The absorbance peak intensity of the colorimetric sensor maintained a good linear relationship in the range of 5 pg/mL to 10 ng/mL, with an LOD as low as 0.5 pg/mL. Wang et al. [75] developed a new colorimetric nano biological platform for the efficient and highly sensitive capture of circulating tumour cells (CTC), in which the MoS_2 NSs surface was modified with two kinds of aptamer functionalized PH sensitive heterochromatic dyes used as a visual detection chip, which had a good PH sensitivity and high dyeing ability.

3.2. Electrochemiluminescence (ECL)

ECL is a special form of chemiluminescence caused by the redox between electrogenerated high-energy radicals [76]. It does not rely on external light excitation and avoids the adverse effects of self-luminous and light scattering [77]. Therefore, it has the characteristics of a precise response, easy control, low noise background signal, high sensitivity, good repeatability, and wide linear range, and has become a powerful tool for biomarker detection and clinical diagnosis in recent years [78][79]. MoS_2 can effectively improve the rate of electron transfer, and it is emerging in the construction of ECL sensing platforms for cancer biomarkers [80]. Zhang et al. [81] used ordered mesoporous carbon-MoS_2 (OMC-MoS_2) as a sensing platform and Cu_2O@OMC-Ru $(bpy)_3^{2+}$ as signal tags to develop a sandwich ECL immunosensor for the detection of AFP. As we know, MoS_2 NSs are easy to agglomerate, resulting in a loss of activity, and the synergistic effect of nanocomposites can offset this loss of activity. OMC exhibits an excellent electrocatalytic performance due to its ordered pore structure, high specific surface area, and high porosity [82]. Therefore, OMC-MoS_2 can synergistically increase the effective surface area and conductivity to improve sensor sensitivity. The ECL detection range of AFP is 0.1 pg/mL–10 ng/mL, with an LOD of 0.011 pg/mL (S/N = 3).

3.3. Fluorescence

Fluorescence analysis is an advanced analytical method with a high sensitivity, selectivity, and practicality, which can qualitatively and quantitatively analyse the changes in fluorescence intensity, emission spectrum, and fluorescence molecular lifetime of substances [83]. Due to the strong adsorption capacity and wide absorption spectrum of MoS_2 NSs to ssDNA, MoS_2 NSs can quench fluorescent groups with different emission wavelengths, showing unique advantages in the construction of fluorescent biosensor platforms [84]. Liang et al. [85] built a fluorescence sensing platform for the hepatocellular carcinoma (HCC) biomarker GP73 based on the Förster resonance energy transfer (FRET). Among them, utilizing the synergistic effect of the MoS_2@rGO composites as a fluorescence receptor further enhanced the quenching effect, and the nitrogen-doped graphene QDs modified by the GP73 aptamer were used as fluorescence donors. The detection range was 5 ng/mL to 100 ng/mL, and the LOD was 4.54 ng/mL (S/N = 3). It also showed a good detection effect in human serum. Wang et al. [86] designed QD molecular beacons (QD-MBs) functionalized with a MoS_2 fluorescent probe (QD-MB@MoS_2) for the dual detection of two kinds of miRNAs related to multiple myeloma (MM), with an LOD as low as the fM level, realizing ultra-high sensitivity detection. In addition, when the MoS_2 crystal becomes very thin, the transition from the indirect bandgap to the direct bandgap will produce a strong fluorescence [87]. MoS_2 QDs have strong quantum confinement and edge effects and other photoelectric properties, and are widely used in fluorescence sensing, catalysis, biological imaging, and other fields [88]. Ge et al., based on the quenching of MoS_2 QDs by the inner filter effect

(IFE) and rolling circle amplification (RCA) technology, constructed a label-free and highly sensitive miRNA fluorescence detection platform with a high selectivity and satisfactory recovery [88].

3.4. Surface Enhanced Raman Scattering (SERS)

SERS technology can provide molecular fingerprint information, has a high sensitivity and specificity, and does not cause damage to the sample, and is thus considered as a promising analytical technology in the field of disease analysis [89]. SERS sensor composition mainly include substrates, target detection substances, and SERS capture probes. MoS_2 has been applied in the preparation of SERS capture probes due to its large specific surface area, stability, and excellent catalytic performance. Engine et al. [90] developed a SERS sandwich immunosensor for the ultra-sensitive detection of AFP. Among them, MoS_2 is modified by the monoclonal antibody as the capture probe of AFP, and its high surface area and adsorption capacity for biomolecules make the sensing interface more stable. The SERS immunosensor based on Au@AgNCs/MoS_2 nanocomposites has a good linear response in the range of 1 pg/mL to 10 ng/mL, with an LOD as low as 0.03 pg/mL. Pan et al. [91] developed a sensitive and direct SERS aptasensor for detecting gastric cancer exosomes. AuNSs-decorated MoS_2 NSs (MoS_2-AuNSs) surfaces were assembled with ROX-labelled aptamers (ROX-Apt) used as nano probes to achieve the ultra-sensitive capture of exosomes. This sensor quantitatively detected gastric cancer exosomes over a wide range of SERS signals (55–5.5 × 10^5 particles/μL), with an LOD as low as 17 particles/μL, which provides a prospective platform for the early diagnosis of gastric cancer. In addition, Hilal et al. [92] developed a sandwich-type SERS immunosensor for the sensitive detection of CEA, which has a good selectivity and stability and is well applied in clinic.

3.5. Surface Plasmon Resonance (SPR)

SPR provides a non-invasive and label-free method to detect analytes. MoS_2 has a large absorption coefficient and high refractive index at 500 nm, whose structure is conducive to the propagation of the surface plasma. Such photoelectric characteristics enhance SPR signals and improve the sensitivity of the sensor [93]. Therefore, the modification of MoS_2 is also applied in SPR sensors for cancer biomarker detection. Chiu et al. [94] prepared MoS_2 by the liquid-phase exfoliation and covalently functionalized it to form carboxyl-functionalized MoS_2 (carboxyl-MoS_2) acting as a signal amplification sensing modification layer. The carboxylation modification effectively improved the sensitivity of the SPR sensor. The SPR chip based on carboxyl-MoS_2 was used to specifically detect the lung cancer-associated biomarker cytokeratin 19 fragment (CYFRA21-1),which shows a wide linear range (0.05 pg/mL–100 ng/mL) and low LOD (0.05 pg/mL), and has a good specificity, selectivity, sensitivity, and affinity. Compared with traditional SPR bare gold chips, the SPR chip has many characteristics, such as a unique glycan matrix structure, high surface area carboxylic acid groups, and excellent biological affinity. In addition to the above sensing methods, other sensing methods based on MoS_2 are listed in **Table 2** to detect various cancer biomarkers.

Table 2. Optical biosensors for cancer biomarker detection based on MoS_2.

Method	Analytes	Electrode/Label	Linear Range	LOD	Ref.
Colorimetry	CEA	Au NPs-MoS_2-Ab2/ CEA/Ab1/MoS_2-Au NPs	5 pg/mL–10 ng/mL	0.5 pg/mL	[74]
Colorimetry	CEA	DNA/MoS_2 NSs	50–1000 ng/mL	50 ng/mL	[73]
Colorimetry	CTC	TP/SYL_3C-MoS_2	5–10^4 cells/mL	2 cells/mL	[75]
ECL	CEA	Ab/MOF-545-Zn@MQDs/GCE	0.18–1000 ng/mL	0.45 pg/mL	[95]
ECL	PSA	GOD-SiO_2-Ab2/PSA /Ab1/MoS_2-AuNPs/GCE	0.5 pg/mL–10.0 ng/mL	0.20 pg/mL	[96]
ECL	HCV gene	S-BN QDs-hairpin DNA2 (H2)/MoS_2 Ns	0.5 pmoL/L–1 nmoL/L	0.17 pmoL/L.	[83]
ECL	HPV 16 DNA	Zn-doped MoS_2 QDs & QD-DNA/reductive Cu(I) particles	0.1–200 nmolL	0.03 nmol/L	[97]
ECL	miRNA-210	S dots/Au NP@MoS_2 NSs	0.1 pM–10 nM	0.03 pM	[98]
ECL	miRNA-21	luminophore/MoS_2 QDs@Zeolitic Imidazolate 2 Framework-8	Buffer (0.1 mM PBS), co-reactant (2 mM H_2O)	14.6 aM	[99]
Fluorescence	CA15-3	DNA/MoS_2 NSs	0.01–0.1 U/mL	0.0039 U/mL	[100]
Fluorescence	PD-1	MoS_2-NFP	125–8000 pg/mL	85.5 pg/mL	[101]

Method	Analytes	Electrode/Label	Linear Range	LOD	Ref.
Fluorescence	miRNA-155 & miRNA-150	QD-MB @MoS_2	10 fM–1 nM	7.19 fM & 5.84 fM	[86]
SERS	CEA	MoS_2 NFs@Au NPs/MBA-Ab2/CEA /Ab1/Fe_3O_4 NPs@Au NPs/ d-Ti_3C_2TX Mxene	0.0001–100.0 ng/mL	0.033 pg/mL	[94]
SERS	CA19-9	R6G-tagged MoS_2 NF	5×10^{-3}–100 IU/mL	3.43×10^{-4} IU/mL	[102]
SERS	exosomes	MoS_2-AuNSs/ROX-Apt	55–5.5×10^5 particles/μL	17 particles/ μL	[93]
SPR	CYFRA21-1	Ab/COOH-MoS_2/Au/Cr/BK7	0.05 pg/mL–100 ng/mL	0.05 pg/mL	[94]

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