MoS$_2$-Based Substrates for Surface-Enhanced Raman Scattering: Fundamentals, Progress and Perspective

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Abstract: Surface-enhanced Raman scattering (SERS), as an important tool for interface research, occupies a place in the field of molecular detection and analysis due to its extremely high detection sensitivity and fingerprint characteristics. Substantial efforts have been put into the improvement of the enhancement factor (EF) by way of modifying SERS substrates. Recently, MoS$_2$ has emerged as one of the most promising substrates for SERS, which is also exploited as a complementary platform on the conventional metal SERS substrates to optimize the properties. In this minireview, the fundamentals of MoS$_2$-related SERS are first explicated. Then, the synthesis, advances and applications of MoS$_2$-based substrates are illustrated with special emphasis on their practical applications in food safety, biomedical sensing and environmental monitoring, together with the corresponding challenges. This review is expected to arouse broad interest in nonplasmonic MoS$_2$-related materials along with their mechanisms, and to promote the development of SERS studies.

Keywords: surface-enhanced Raman spectroscopy; MoS$_2$; two-dimensional materials; charge transfer

1. Introduction

SERS is an effective spectroscopic technique for the detection and analysis of molecules adsorbed on rough metal surfaces or other nanostructures with high sensitivity and accuracy [1]. It was first observed due to the miraculous increase in signals of surface-enhanced Raman spectra of pyridine adsorbed on electrochemically rough silver in 1973, 45 years after the first discovery of Raman scattering [2]. Since then, the scope of SERS has been gradually broadened due to its characteristics such as high sensitivity and selectivity, rapid measurement, fingerprint characteristics, nondestructive examination, and good biocompatibility (Figure 1a). Numerous experiments have been carried out to explain the mechanism of enormous signal enhancement. It was not until the proposal of electromagnetic mechanism (EM) and chemical mechanism (CM) in 1977 that the reinforcement mechanism of SERS was basically formed and well acknowledged [3,4]. Later, as more newly fabricated materials were applied as SERS substrates, the reinforcement mechanism was gradually refined and has become the important focus of theoretical research on SERS [5,6].

The conventional substrates for SERS were some surface-roughened noble metals such as gold, silver and copper [7,8]. There are two main ideas to improve detection accuracy and expand the application scope of metal substrate for SERS: (1) moving concentration from precious metals to transition metal nanoarrays [9–12] and (2) changing the configuration and shape of Au/Ag nanoparticles (Au/Ag NPs) [13,14], such as Au nanocube array [15], concave–convex nanostructure array [16], checkerboard nanostructure [17], among others [18,19] (Figure 1b).

Another research idea is to combine different kinds of materials to exploit the advantages of diverse materials jointly and achieve better performance in various aspects [20,21]. At present, with two-dimensional (2D) materials flourishing, researchers are attempting to
utilize these materials as substrates for SERS. Some of these 2D semiconductor materials are emphasized for their high chemical stability, good biocompatibility and controllability during fabrication [22–24]. Among them, MoS2 emerges as one of the most promising materials as a new platform for SERS research owing to its extraordinary adsorption capacity and fluorescence quenching ability [25,26]. Moreover, MoS2 has its apparent merits in photoelectric devices, electrochemistry and biosensors [27]. The band gap of MoS2 can be adjusted from 1.29 to 1.9 eV as the number of layers increases, demonstrating its flexibility and light absorption [28]. Although the SERS enhancement factor of a single pristine MoS2 monolayer is relatively small, its combination with metal nanoparticles can overcome the weak adsorption capacity and aggregated oxidation of a single metal substrate [29,30].

![Figure 1](image_url)

**Figure 1.** (a) Features of SERS; (b) development of research on SERS substrate; (c) schematic of Raman scattering; (d) EM: surface plasmon resonance on metal surface; (e) CM: charge transfer between analyte molecules and roughed substrate.

In this review, we begin by introducing the fundamentals of SERS, including two commonly accepted SERS mechanisms and MoS2-related SERS mechanisms. Then, several basic synthesis methods, advances and multitudinous applications of MoS2-based substrates are discussed. Finally, we summarize the current situation of SERS centered on MoS2 material and look forward to its development trend. We hope this review encourages broad interest and sheds light on the synthesis and application for SERS with high sensitivity.

2. Fundamentals of SERS

2.1. SERS Mechanism

Raman scattering was first discovered in 1928 and refers to the change in frequency of a light wave when it is scattered. When light is scattered from an atom or molecule, most
photons are elastic scattering, also known as Rayleigh scattering, meaning that the photons have the same frequency before and after scattering [31]. However, a small part (about $10^{-10}-10^{-6}$) of the photons changes in frequency, namely Raman scattering (Figure 1c), and SERS is based on Raman scattering.

EM is considered the leading cause of the SERS phenomenon, represented by the surface plasmon resonance (SPR) model of the metal (Figure 1d), which has a long-range effect and has little to do with the type of adsorbent molecules [32–35]. Surface plasmons were first observed in the spectrum of light diffracted on a metallic diffraction grating. It was soon proven that the anomaly was associated with the excitation of electromagnetic surface waves on the surface of the diffraction grating [36]. It was recognized that under the action of the photoelectric field, electrons near the metal surface would produce dense vibrations, causing excitation of the plasmons, especially on a rough surface [37]. Once the incident light frequency matches the oscillation frequency of electrons near the metal surface, a local surface plasma resonance occurs. Then, the electromagnetic field in the vicinity of the nanoparticles is significantly enhanced [38]. The electromagnetic enhancement also includes the image field enhancement [39] and tip lightning rod effect [40], though their contribution is smaller than the SPR mentioned above.

CM refers to the charge resonance transition generated by the interaction between molecule and substrate (Figure 1e), as well as charge transfer between analyte molecules. Unlike EM, CM has a short-range effect and mainly depends on the type of adsorbent molecules and the interplay between detected molecules and the substrate [41,42]. Because of the complexity of the substrate and the detection of molecular species, CM is far more complicated than EM [43].

CM primarily suggests that electrons in the metal are excited to the charge-transfer state under laser irradiation of appropriate wavelength, which causes relaxation of the molecular nuclear skeleton. Therefore, when the electron returns to the metal, the photon emitted is one less vibrational quantum of energy than the incoming light. The enhancement is caused by the resonance of the scattering process with the charge-transfer state [44].

2.2. MoS$_2$-Related SERS Mechanism

It was proven that the EF of 2D monolayer MoS$_2$ as SERS substrate to detect 4-Mercaptopyridine could reach $10^5$, much higher than the previous observation on 2D graphene and boron nitride [45]. This considerable enhancement in the SERS signal is probably attributed to interface dipole interaction and the enhanced charge transfer from 2D MoS$_2$ to organic molecules when in resonance [46]. Although the enhancement mechanism of the metal/MoS$_2$ composite substrate is not well understood, theorists generally believe that both EM and CM make contributions.

One of the more plausible explanations is that since the Fermi level of MoS$_2$ is higher than that of Au nanoparticles, Au nanoparticles act as the electron capture centers in the conduction band of MoS$_2$, resulting in the transfer of electrons from MoS$_2$ to Au. Therefore, potential changes and the formation of the Schottky barrier occur on the surface of MoS$_2$ (Figure 2a,b). This process, together with the electromagnetic enhancement of Au nanoparticles, remarkably enhances the Raman signal [47].

Another explanation takes the more general interaction between semiconductors and metals into account and suggests that light exposure plays a crucial role in enhancing the Raman signal. In this course, two conditions may contribute to signal enhancement. First, owing to the localized surface plasmon resonance (LSPR) of metal nanocrystals, local enhanced electromagnetic fields are generated on the surface (the gray areas in Figure 2c,d). When the metal nanocrystals are close enough to MoS$_2$, the local electromagnetic field and the absorption spectrum of MoS$_2$ overlap, which promotes the electron transfer from the valence band to the MoS$_2$ conduction band and generates electron-hole pairs (Figure 2c). Because of the strong field of the metal nanocrystals, the intensity of this process is increased by several orders of magnitude relative to light alone. During their interaction, the enhancement effect of the Raman signal is further amplified. The other functioning mecha-
nism is related to plasmonic sensitization. In simple terms, the laser-induced plasmonic sensitization excites electrons in the conduction band of metal nanocrystals to overcome the Schottky barrier and jump into the conduction band of MoS₂ (Figure 2d). The electromagnetic and chemical enhancements are amplified by plasma excitation and electron transfer during the entire process.

![Diagram](image)

**Figure 2.** (a,b) Schematic diagram of Fermi level movement of Au/MoS₂ hybrid SERS substrate. Reprinted with permission from ref. [48]. Copyright 2014 Springer Nature. (c) Mechanism for plasmonic enhancement of light absorption. (d) Mechanism for plasmonic sensitization and electron excitation from the metal nanocrystal to MoS₂.

### 3. Hybrid SERS Nanostructures Based on MoS₂

#### 3.1. Synthesis of MoS₂-Related SERS Substrates

Different research groups have prepared MoS₂-based SERS substrate using diverse methods. They have found differences in the final enhancement effect through comparison, which implies that preparation technology can influence the efficiency and detection sensitivity of SERS to some extent [49–54]. The preparation methods of SERS substrates have been constantly updated and developed with the development of preparation technology. In the following, we describe some classical preparation methods and discuss the effect of impurities and defects introduced during the preparation process on the detection limits.

#### 3.1.1. Synthesis of MoS₂

Currently, there is a wide variety of preparation technologies for SERS substrates to MoS₂. The following are some traditional approaches, namely the hydrothermal/solvothermal method, chemical vapor deposition (CVD) method and mechanical force stripping method.

**Hydrothermal/Solvothermal Method**

The hydrothermal/solvothermal method uses molybdenum-containing compounds as molybdenum sources and high-purity sulfur compounds as sulfur sources and surfactants. These two are mixed by reaction, and the liquid sample mixture is acquired after complete stirring. The mixture is then dried, heated and molded through a closed-kettle under high temperature (Figure 3a). In the sealed heating process, MoS₂ substrates with different morphologies can be obtained by controlling the reaction time, temperature and the number of reaction reagents. For instance, Jiang et al. [55] used Na₂MoO₄·2H₂O (molybdenum
sources), CH$_3$CSNH$_2$ (sulfur sources) and H$_4$[Si(W$_3$O$_{10}$)$_4$] $\times$H$_2$O to collect deposited MoS$_2$ in the autoclave. It was employed as SERS substrate to detect carbohydrate antigen 19-9 in serum directly, and the final minimum detection concentration reached $10^{-14}$ mol·L$^{-1}$ level.

Chemical Vapor Deposition (CVD)

The CVD method is one of the traditional methods for the preparation of large-area nanofilm materials [56]. After decades of technical innovation, it is considered a mature technology for preparing 2D nanofilm materials [57,58]. The preparation process involves placing the growth base in a CVD tubular furnace, passing it through the precursor gas and allowing it to react on the surface of the substrate [59]. In preparing MoS$_2$ nanosheet films by the CVD method, Mo is first sputtered on SiO$_2$ substrate, then MoS$_2$ nanometer-thin films are grown on the surface through the reaction between Mo and sulfur vapor in the furnace. The size and thickness of the MoS$_2$ substrate can be modulated artificially by altering the thickness of Mo metal films. Zhan and colleagues [60] used this method to deposit Mo on the SiO$_2$ substrate surface and fabricated a MoS$_2$ thin-film layer by heating sulfur powder and reacting with Mo at a high temperature. Zheng et al. [61] used electrochemically oxidized Mo foil as a growth material to achieve layer-by-layer growth of MoS$_2$ by rapid sulfidation of Mo oxides in the gas phase (Figure 3b).

Mechanical Stripping Method

The mechanical stripping method applies the viscosity of special tape to act on the surface of MoS$_2$ material to weaken Van der Waals forces of MoS$_2$ between layers (Figure 3c). Without breaking the covalent bond, MoS$_2$ layered structure or even a single layer structure can be obtained. The thin layer is attached to the SiO$_2$/Si substrate surface to form a MoS$_2$ substrate. Yan et al. [62] obtained MoS$_2$ substrate for Rh6G molecule detection with a minimum detection limit of $10^{-8}$ mol·L$^{-1}$ by the mechanical stripping method combined with heating and annealing treatments.

![Figure 3.](image_url)

Figure 3. (a) Schematic of hydrothermal method to fabricate MoS$_2$ nanoflowers. Reprinted with permission from ref. [63]. Copyright 2018 Elsevier. (b) CVD growth of MoS$_2$ flakes using arched oxidized Mo foil as precursor. Reprinted with permission from ref. [61]. Copyright 2017 John Wiley and Sons. (c) The flowchart of the mechanical stripping method to prepare 2D MoS$_2$. 
3.1.2. Synthesis of Metal/MoS\textsubscript{2} Hybrid Substrate

Recent approaches to prepare metal/MoS\textsubscript{2} hybrids substrates for SERS can be organized into three categories: (1) physical methods: physically depositing specific metal on MoS\textsubscript{2} or placing ready-made metal nanoparticles on MoS\textsubscript{2} directly; (2) chemical methods: spontaneous reduction method, self-assembly technology, thermal reduction method (including hydrothermal method, solvothermal method, microwave-assisted hydrothermal method), among others; (3) nanoetching methods: plasma etching, electron beam lithography (EBL) and photoetching. We emphatically describe the latter two approaches in this part.

Spontaneous Reduction Method

The spontaneous reduction method refers to the initiative reduction reaction between the prepared MoS\textsubscript{2} film and the precursor solution of metal nanoparticles such as HAuCl\textsubscript{4} solution (the precursor of gold NPs), to obtain directly the metal/MoS\textsubscript{2} composite substrate. This spontaneous reduction can occur at room temperature or more uniformly and rapidly through auxiliary means such as heating [50,64].

For example, in a typical preparation method, the concentrations of HAuCl\textsubscript{4} significantly influence the character of the Au NPs-loaded MoS\textsubscript{2} surface and eventually the Raman EF. As the concentration of the precursor HAuCl\textsubscript{4} increases, the Au NPs on the AuNPs@MoS\textsubscript{2} show more hotspots and more aggregation, and the detection limit of AuNPs@MoS\textsubscript{2} for Rh6G decreases and then increases [50]. Therefore, too high or too low precursor concentration is not conducive to the SERS enhancement effect of the hybrid substrates, and the regulation of selecting the appropriate HAuCl\textsubscript{4} concentration has become one of the main concerns of the experimentalists.

Hydrothermal Reduction Method

Hydrothermal reduction is the process of reducing metal cations in solution under different conditions while adding MoS\textsubscript{2} material. The cations are attracted by unsaturated sulfur on the MoS\textsubscript{2} surface to form chemical bonds, and eventually the metal/MoS\textsubscript{2} composite SERS substrate is obtained. Singha’s group [63] adopted the hydrothermal method to modify MoS\textsubscript{2} with Au NPs and detected free bilirubin in human blood, which showed high sensitivity, stability and good reproducibility. However, compared with the traditional hydrothermal method, the microwave-assisted hydrothermal method is more frequently used to prepare nanomaterials [50,65,66]. Microwaves are utilized as a heating tool to realize stirring on the molecular level. It overcomes the shortcoming of uneven heating in the hydrothermal vessel, thus shortening reaction time and improving efficiency [67–69]. Kim and coworkers [70] reported this facile method and observed that the gold nanoparticles tend to grow at defective sites, mainly at the edges and the line defects in the basal planes.

During a hydrothermal reaction, flowing high purity argon is usually used to avoid oxidation during the reaction, which greatly affects the SERS sensitivity of the final substrate [63]. According to Kim’s work, the chemical intercalation–exfoliation process in the hydrothermal method created more defects in the substrate surface of MoS\textsubscript{2} flakes than its single-crystal counterpart when preparing MoS\textsubscript{2}, which facilitated the deposition of higher density gold nanoparticles [70]. The Au NPs@MoS\textsubscript{2} obtained by this method ultimately exhibited better enhancement and lower detection limits.

Nanoetching Method

Nanoetching technology was first applied in the integrated process and had irreplaceable advantages in micrographics [71]. Its advantages such as fast processing speed, high precision, minor damage to substrates and no pollution make it a popular technique.

The typical representative of electron beam processing is electron beam lithography (EBL), which mainly uses electron beams to induce surface reaction beams for microprocessing. The reaction between the atoms on the substrate surface and the adsorbed molecules
or ions is facilitated by irradiating the specimen by the electron beam, and the designed pattern is finally obtained on the substrate by the liftoff technique. Zhai et al. [72] applied EBL to fabricate a Au nanoarray on the monolayer MoS$_2$ film, which was used as a SERS substrate to realize CV detection of $10^{-6} - 10^{-15}$ M. They considered it to be combined with the separation technology to form a sensor that can quickly detect trace molecules in a natural environment.

The focused laser beam can locally transform the MoS$_2$ film into microscopic patterns with active nucleation sites. When the modified film is in complete contact with the reaction substance, selective modification can be achieved at specific locations to flexibly prepare a thin layer of MoS$_2$ decorated by metal NPs. Lu and coworkers [73] employed this technology to realize self-designed pattern preparation of Au NPs decorating MoS$_2$. They controlled the localized modification of the materials by changing the laser power, MoS$_2$ film thickness and reaction time. It was proven that the prepared hybrid substrate can detect aromatic organic molecules with outstanding performance.

The femtosecond laser is another technique that is widely adopted to modify MoS$_2$ with metal NPs [51,53]. It can induce photoelectrons generated on the film surface and greatly promote the interaction between metal cations and photoelectrons on the film surface. Then, the reduction and in situ deposition of metal NPs on MoS$_2$ nanosheets formed the metal/MoS$_2$ hybrid substrates for SERS.

Nanoetching technology possesses unique advantages in terms of precise tuning. The roughness of the laser-treated MoS$_2$ film is about three times greater than that of the pristine, which facilitates the deposition of metal nanoparticles [73]. The hybrid substrates prepared by this method show stronger SERS activity, whose detection limit can reach as low as 1 fM for CV detection. In addition, the power of the laser also affects the Raman intensity at the same concentration of the analytes [72].

3.2. Advances in MoS$_2$-Based SERS Substrate

3.2.1. MoS$_2$ Substrates

With the development of chemical mechanisms, SERS substrate material is not confined to metal, and MoS$_2$ emerges as a promising substrate material owing to its distinct merits shown in SERS studies. For single MoS$_2$ material research, researchers have placed more focus on 2D material, which can be roughly divided into two directions: (1) special treatment of MoS$_2$ material, such as plasma treatment and usage of the femtosecond laser to induce defect sites on the surface to enhance the charge transfer; and (2) stacking the single-layer 2D MoS$_2$ material according to the set angle to obtain double-layer MoS$_2$.

For the former research direction, it was found that the plasma-processed MoS$_2$ nanosheets can perform better in SERS. The Raman intensities of Rh6G on MoS$_2$ nanoflakes were enhanced more than tenfold after oxygen-plasma and argon-plasma treatments [74]. Other external treatments such as pressure and femtosecond laser were verified that they could reinforce charge transfer between the substrate and molecules to induce MoS$_2$ defect sites and realize pressure or photoluminescence control [75–77]. Sun et al. [77] found that there are more transferred charges between the substrate and analytes with increasing applied pressure (Figure 4a), which also leads to an increase in the enhancement factor. For the latter, Xia and coworkers [78] studied prominent resonance Raman and photoluminescence spectroscopic differences between AB ($60^\circ$, Figure 4c) and AA' ($0^\circ$, Figure 4d) stacked bilayer MoS$_2$, and considered that the $0^\circ$ stacked MoS$_2$ bilayer was superior to the $60^\circ$ stacked one in interlayer electron coupling, hence its Raman enhancement effect was more outstanding (Figure 4b).

Compared with metal, MoS$_2$ possesses unique adsorption capacity, especially for some aromatic molecules, because the $\pi$ bonds of MoS$_2$ interplay with those of aromatic molecules [73,79]. Furthermore, MoS$_2$ has good fluorescence quenching ability and can quench background fluorescence, which is conducive to detection and substrate stability at low concentration [26,80]. However, its electromagnetic enhancement is extremely weak, and chemical enhancement alone can hardly contribute significantly to sensitivity.
In addition, owing to the selectivity and complexity of chemical enhancement for the detection of molecules, these substrates can only be implemented for some particular organic molecules such as aromatic molecules.

Figure 4. (a) Charge transfer at the monolayer MoS\(_2\) (ML-MoS\(_2\))/methylene blue (MB) interface varies with pressure. The charge gained by ML-MoS\(_2\) and the charge lost by MB molecules are set to be positive and negative, respectively. Reprinted with permission from ref. [76]. Copyright 2021 American Chemical Society. (b) Resonance Raman spectra of monolayer and bilayer MoS\(_2\) on Au nanoprisms. Reprinted with permission from ref. [78]. Copyright 2015 American Chemical Society. Atomic structure diagram of (c) AB and (d) AA' staked bilayer MoS\(_2\) (purple balls represent Mo atoms, and yellow balls represent S atoms). Reprinted with permission from ref. [78]. Copyright 2015 American Chemical Society.

3.2.2. Metal/MoS\(_2\) Hybrid Substrates

Metal/MoS\(_2\) hybrid substrates are considered admirable SERS substrates, with EFs that can reach 10\(^8\) and even up to 10\(^{12}\) after some special processing such as changing shape and metal nanoparticles configuration [81]. Because of the prominent enhancement effect of this substrate, experimentalists have conducted various studies on it, making this kind of substrate become one of the important research topics of SERS in recent years.

One was on Au NPs /MoS\(_2\), and the researchers found that these composite substrates enhanced significantly better than either single Au or single MoS\(_2\). Subsequently, Rani et al. [82] used low-power focused laser cutting to carve artificial edges on the MoS\(_2\) monolayer. The intensive accumulation of Au NPs along the artificial edges led to the aggregation of SERS hotspots in the same places, which made it possible to generate SERS hotspots with ideal location and geometry shape in a controllable way on a large-area substrate (Figure 5). Liang’s group [83] prepared 3D MoS\(_2\)-nanospheres, 3D MoS\(_2\)-nanospheres @Au seeds and 3D MoS\(_2\)-nanospheres @Ag-NPs hybrids structures, and calculated their enhancement factors as 500, 7.5 \times 10^8 and 1.2 \times 10^9, respectively.
Through experiments, they believed that silver nanoparticles were more suitable than gold nanoparticles as modification materials for MoS$_2$. This is because silver nanoparticles can be closer to each other and have higher coverage, leading to more hotspots on the surface and stronger signal enhancement.

![Figure 5](image_url)

**Figure 5.** (a) Raman peaks of Rhodamine B (black dotted line) and signature signals of MoS$_2$ (red and green dotted line) and Si (yellow dotted line), obtained at the edge of laser-etched MoS$_2$ surface modified with Au NPs. (b–i) Micromapping images of a star-shaped feature at characteristic peaks of MoS$_2$, Si and Rhodamine B, illustrating localized hotspots generated along the factitious edges of the star-shaped nanostructure. Reprinted with permission from ref. [82]. Copyright 2020 American Chemical Society.

Compared with the substrates mentioned above, the metal/MoS$_2$ hybrid substrate concentrated the advantages of metal and MoS$_2$, so it shows better adsorption effect, higher sensitivity, stronger stability and lower detection limit, and has gradually become a new platform in SERS research. Because of the modification of MoS$_2$ by metal nanoparticles, the composite substrate exhibits not only stronger electromagnetic enhancement, but also better chemical enhancement effect and fluorescence quenching effect, which can greatly reduce external interference. However, owing to the unclear mechanisms of the interaction between metal and MoS$_2$ and the complicated production process, further development of this kind of substrate has been limited to some extent.

### 3.3. Practical Applications

Most organics have SERS activity and their molecules are very close in size to the analytes in the plasmonic structure, making SERS very suitable for the detection of these small molecules. Furthermore, SERS is promising to become a viable alternative to mass
spectrometry and chromatographic-based techniques, owing to its potential for high sensitivity, specificity and capability of rapid measurements. In this section, we mainly focus on SERS technique applications such as food safety detection, biomedical sensing and environmental monitoring, particularly examining MoS$_2$-based SERS.

3.3.1. Food Safety Detection

Food issues have always been a concern, and there have been numerous reports of excessive additives found in food. Therefore, a sensitive and credible approach for detection techniques is imperative. Since most illegal additives have Raman activity, the SERS technique can examine their contents, ensuring powerful food supervision [84–86]. Li et al. [87] prepared a 3D flexible Ag NPs@MoS$_2$/pyramidal polymer structure, which not only had a large surface area but also could generate dense hotspots. The minimum detection limits of the structure reached $10^{-13}$ and $10^{-14}$ M for Rh6G and CV as probe molecules, respectively, which showed the ultrasensitivity of the structure. Long-term repeated use experiments showed the stability and reproducibility of the structure. In addition, they used the structure to achieve ultralow in situ detection of melamine in milk with a measured detection limit of $10^{-6}$ M, which was found to be within the safe range according to FDA regulations.

The detection of pesticide and antimicrobial residues on food is also the main interest for SERS in food safety. Therefore, some researchers have detected the residues by MoS$_2$-based SERS. Chen and coworkers [88] developed an Ag NPs-MoS$_2$ composite substrate with striking SERS activity and photocatalytic efficiency. They established two calibration curves with ultralow detection limits of $6.4 \times 10^{-7}$ and $9.8 \times 10^{-7}$ mg/mL for the standard solutions of tetramethylthiuram disulfide (TMTD) and methyl parathion (MP). Finally, they successfully achieved a recyclable detection of single and mixed residues of TMTD and MP on eggplant, Chinese cabbage, grape and strawberry by using different monitoring protocols depending on the size and level of surface roughness (Figure 6). Zhai et al. [72] prepared Au nanodisk array-monolayer MoS$_2$ (ADAM) composites material by EBL technique. They experimentally demonstrated the good stability of the composite at different laser frequencies and temperatures. According to their research, the ADAM composite material was highly sensitive as a SERS substrate, enabling CV detection in the range of $10^{-6}$–$10^{-15}$ M with detection limits as low as 1 fM. They also used this active substrate continuously for the detection of antimicrobial residues in aquatic products and found it under the safety limits of the EU directive.

However, it is still challenging for SERS to achieve in situ analysis of toxic residues in real foods due to the complexity of real foods and the low concentration of contaminants. Therefore, how to further improve the sensitivity of SERS detection and realize the combination with rapid separation techniques needs to be further explored.

3.3.2. Biomedical Sensing

SERS promises to be a viable alternative in the field of bioanalytical sensing due to its numerous merits mentioned above and its potential to be integrated into small packages for measurement at the point of care, which can be used for clinical testing to cure some intractable diseases [89–92]. At present, SERS is mainly applied for three aspects in biomedical sensing: (1) analyzing the properties of biomolecular components, (2) effectively detecting target substances in various mixtures and (3) cell imaging.

For biomolecular analysis, Guerrini et al. [93] performed label-free analysis of unmodified dsDNA by SERS using positively charged silver colloids. The electrostatic adhesion of DNA promoted the aggregation of nanoparticles into stable clusters, producing intense and reproducible SERS spectra at the nanoscale. Based on this, they reported the quantitative identification of hybridization substances, along with SERS identification of single base mismatches and base methylation (5-methylated cytosine and N6-methylated adenine) in duplexes. Moreover, when a SERS probe is scaled down to a quantum scale, it is possible to study epigenetic features of cancer stem cells and gene expression aberrations in genomic
DNA. Ganesh et al. [94] performed experiments based on this principle, pointing out differences in genomic DNA between cancer and noncancer cells, and achieved tracking of both genes. For the tracking detection aspect, Singha and coworkers [63] used Au NPs/MoS2 nanoflower hybrid as a SERS substrate, which used Rh6G as a probe molecule with detection limits as low as 10−12 M. This SERS biosensor detected free bilirubin under the interference of key interfering factors such as glucose, cholesterol and phosphate in human serum, showing good selectivity and reliability, as well as potential for clinical diagnosis. For medical imaging, Fei et al. [64] fabricated gold nanoparticles@MoS2 quantum dots (Au NPs@MoS2 QDs) core-shell nanocomposite. The pinhole-free, chemically inert and ultrathin MoS2 QDs shell protected the Au core from the chemical environment and probe molecules. The detection limit of this hybrid substrate for crystal violet could reach 0.5 nM. In addition, the hybrid was also used as a nanoprobe for label-free near-infrared SERS imaging of 4T1 cells. Finally, they successfully obtained distinguishable SERS images from 4T1 cells.

![Figure 6](image_url). Recyclable SERS-based detection on eggplant (denoted as 1), Chinese cabbage (2), grape (3) and strawberry (4); first cycle for (a) TMTD and (b) MP and second cycle for (c) TMTD and (d) MP. Reprinted with permission from ref. [88]. Copyright 2020 American Chemical Society.

However, there are certain challenges in the application of SERS in biomedicine. Because of the complex structure of biological macromolecules, elastic scattering may occur in all directions from all parts of the cell. Elastic scattering generates severe background signals on the SERS spectra, which seriously interferes with the analysis and detection. Therefore, how to optimize the SERS probe, reduce the risk of signal interference in SERS detection and enhance its screening capability will be the focus of research for this application.

3.3.3. Environmental Monitoring

With the development of modern industry, environmental pollution has become a problem that cannot be ignored. Some organic pollutants can enter our food chain through water pollution and soil pollution, posing a severe threat to our health and adversely affecting the balance of the ecosystem. Therefore, using simple and accurate measurement methods to monitor the environment has become the focus of our attention. SERS has been applied to detect the water environment and soil owing to its various merits.

Zhao et al. [95] prepared a PSi/MoS2/Au NPs MSC (pyramidal Si/MoS2/Au NPs multiscale cavity), and they used this hybrid substrate to detect CV alcohol solutions from 10−5 to 10−10 M, and found that the main characteristic peaks were still evident when the concentration reached 10−10 M. They used PSi/MoS2/Au MSC and PSi/MoS2
MSC to determine the hydrophilic and hydrophobicity of the mixtures with different concentrations, respectively, to compare and analyze the superiority of PSi/MoS₂/Au MSC compared to PSi/MoS₂ MSC (Figure 7a,b). Through experiments, they reported that PSi/MoS₂/Au MSC can achieve targeted monitoring of organic contaminants and act as a visible-light self-cleaning SERS substrate with good recovery properties. In addition, a Cu/CuO @Ag nanowire complex that transforms from hydrophilic to hydrophobic under infrared light was prepared as a multifunctional SERS substrate [96]. The substrates have controlled wettability and can self-separate in multiphase solutions and adsorb to the two terminals of the substrate. Malachite green and formalin were used as two probe molecules at two different terminals to obtain the lowest detection limits of 10⁻⁹ M and 10⁻⁵ M. The substrate, after complete hydrophobic modification, can also be used to extract the organic phase (Figure 7c) in “oil/water” mixtures and as a probe for in situ detection.

However, there are still some difficulties. Because of the reality that wastewater is a heterogeneous solution, organic contaminants are often heterogeneously distributed in it, which leads to inaccurate collection of Raman signals. In addition, for some heavy metal ions in the environment, the SERS technique cannot be used directly for detection, but requires further modification of the probe to enable indirect detection. These difficulties need to be further refined.

Figure 7. (a) The SERS spectra of Rh6G aqueous solution (10⁻⁵ M), Sudan 1 toluene solution (10⁻³ M) and their mixture detected from PSi/MoS₂ MSC. (b) The SERS spectra of Rh6G aqueous solution (10⁻⁹ M), Sudan 1 toluene solution (10⁻⁵ M), and their mixture detected from PSi/MoS₂/Au MSC [95]. (c) Extract toluene from the mixed “water/toluene” solution by hydrophobic Cu/CuO @Ag substrate. Reprinted with permission from ref. [96]. Copyright 2020 Elsevier.

4. Conclusions

In this minireview, the superiority of MoS₂-based substrate is emphasized, because these kinds of substrates possess characteristics such as solid fluorescence quenching effects and adsorption abilities. These advantages can make up for the deficiency of roughened metal. The probable mechanisms of MoS₂-based SERS are depicted in detail,
mainly attributed to the enhanced charge transfer. Then, we introduce the synthesis, advances and practical applications of MoS$_2$ and metal/MoS$_2$ hybrid substrate in sequence. The search or modification of SERS substrates, such as changing the shape, nanoparticle configuration and unique surface treatment, to improve EF and lower detection limits has been the focus of experiments. Refinement of existing enhancement mechanisms can contribute to establishing the direction of SERS substrate pursuit and modification. It is worth mentioning that although EM and CM are sufficient to explain most of the existing phenomena, they still need further improvement, which will become the emphasis of future research.

In recent years, the combination with a wide range of technologies such as rapid separation techniques has been essential to broaden the scope of SERS applications. However, SERS substrates prepared by conventional methods may exhibit problems such as heterogeneity and instability, which may limit the development of this technology and its widespread application. Thus, how to design an optimal synthesis method to achieve high reproducibility and mass production also becomes a focus in the future. In terms of application, it is evident that the application of SERS technology in the field of bioscience has become a general trend. In addition to the detection and analysis of biomarkers mentioned above, the technology can also be used in assisted tumor location, protein analysis, etc., which will greatly benefit humanity. In conclusion, MoS$_2$ has served as a new platform for SERS research, but the future development and application prospect of this material deserve further exploration.

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