RSC Advances

ROYAL SOCIETY OF CHEMISTRY

REVIEW

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Cite this: *RSC Adv.*, 2026, **16**, 29249

Research progress of surface-enhanced Raman scattering sensors for the detection of antibiotic residues in food and environment: mechanism, substrate design and challenges

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Received 10th March 2026
Accepted 11th May 2026

DOI: 10.1039/d6ra02048h

rsc.li/rsc-advances

Surface-enhanced Raman scattering (SERS) technology shows great potential for on-site detection of antibiotic residues in food and environmental matrices due to its high sensitivity, rapid response, and unique molecular fingerprint recognition capability. This article systematically reviews the latest research progress of SERS antibiotic sensors, focusing on four aspects: enhancement mechanisms, substrate design strategies, practical application challenges, and future directions. First, starting from the basic principles of electromagnetic enhancement and chemical enhancement, the milestone work of single-molecule SERS is introduced, and the guiding role of density functional theory calculations in revealing the relationship between antibiotic adsorption orientation and signal intensity is discussed. Second, the design strategies from metal nanoparticles to composite substrates are summarized, with particular emphasis on the advantages of carbon materials and two-dimensional materials hybridized with metal/metal oxide substrates in synergistic enhancement and anti-interference. Then, the system analyzed the three major core challenges hindering the practical application of SERS sensors: matrix interference from complex samples, difficulty in selective recognition of structurally similar antibiotics, and insufficient reliability and reproducibility of signal quantification. In response to these challenges, this paper summarizes solutions such as surface functionalization, molecular imprinting/aptamer modification, internal standard methods, and uniform substrate preparation. Finally, the future development directions of this field were envisioned, including the integration of SERS with microfluidic chips to achieve automated sample pre-treatment, machine learning-assisted spectral data analysis, and the standardization and cost control for commercial portable sensors. This review aims to provide theoretical guidance for the design of high-performance SERS antibiotic sensors and promote their practical application in food safety and environmental monitoring.

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1. Introduction

1.1 Global challenges of antibiotic residues

In the context of globalization, antibiotic residues have emerged as a critical global challenge. With the expansion of industrialized farming, the popularization of medical antibiotic use and the imperfection of wastewater treatment facilities, antibiotic residues have become pervasive in our daily lives, infiltrating food supply chains, natural water bodies, soil ecosystems, and air environments.[1] These residual antibiotics not only cause non-negligible damage to the ecosystem but also silently threaten human health and promote the spread of antibiotic resistance, which has become a major problem in the field of global public health.[2,3]

Within the food industry, the issue of antibiotic residues is especially pronounced. Antibiotics are extensively employed in industrial farming to prevent diseases, control infections, and enhance growth rates. However, these antibiotics are not completely metabolized by animals, but are excreted into the environment or directly remain in animal-derived foods such as meat, dairy products and eggs. The long-term intake of food containing antibiotic residues by consumers may cause allergic reactions and destroy the balance of human intestinal microbes, leading to the colonization of antibiotic-resistant bacteria in the human body and weakening the effectiveness of antibiotics in the treatment of infectious diseases.[4] This potential risk is more pronounced, especially in children, pregnant women, and immunocompromised populations, and may have a long-term negative impact on their health.[5–7]

Antibiotic residues in the environment cannot be ignored.[8] As an important source of antibiotic emissions, wastewater treatment plants cannot completely remove antibiotics from wastewater owing to the limitations of the treatment processes. These antibiotics are then discharged into natural water bodies, such as rivers and lakes, causing toxic effects on aquatic organisms, interfering with their normal physiological functions and ecological behaviors, and even affecting higher trophic organisms, including humans, through the food chain.[9–11] Agricultural irrigation and land use of livestock and poultry manure also cause antibiotics to enter the soil ecosystem, change the soil microbial community structure, and reduce soil fertility, thus adversely affecting the growth and quality of crops.[12–14] In the atmospheric environment, antibiotic residues are spread through the air, further expanding their scope of influence, making it difficult to isolate them even in remote areas.

Faced with this global challenge, analytical chemistry, as a vital scientific discipline, bears a mission-critical responsibility. Accurate and sensitive detection of antibiotic residues is a prerequisite for effective monitoring and control of its spread. Conventional detection methods, such as high-performance liquid chromatography (HPLC),[15,16] gas chromatography-mass spectrometry (GC-MS)[17,18] and enzyme-linked immunosorbent assay (ELISA),[19–21] can detect antibiotic residues to a certain extent, but these methods also have limitations. For example, HPLC and GC-MS require complex sample pretreatment processes, including extraction, purification, and derivatization, which are not only time-consuming and laborious, but also introduce human errors, resulting in inaccurate test results. In addition, these techniques usually require professional operators and expensive equipment, which is impractical for on-site rapid detection and real-time monitoring.[22] Although immunoassay methods such as ELISA are relatively simple to operate, their detection sensitivity and specificity are limited, and they easily interfere with the sample matrix, resulting in

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false-positive or false-negative results.[23,24] These technical bottlenecks severely limit the application of detection methods for the detection of antibiotic residues in food and the environment. There is an urgent need to find more efficient, sensitive, and convenient detection methods to meet actual needs. It is urgent to find more efficient, sensitive and convenient detection methods to meet the actual needs. More seriously, the existing technical systems usually require tedious pretreatment steps when dealing with complex matrix interferences (such as lipids in meat and humic acid in environmental water samples), which seriously restricts the realization of rapid on-site detection. Therefore, the development of new detection techniques that can meet the actual needs has become a research "hot spot" in the field of analytical chemistry.

1.2 Introduction of SERS technology

In 1928, Indian physicist C. V. Raman first discovered that when monochromatic incident light is incident on an object, there are scattered light with different frequencies in addition to the Rayleigh scattering with the same frequency as the incident light. This type of scattered light with different frequencies was later called Raman scattering. Studies have shown that the intensity of Rayleigh scattering light is only 10^{-3} of the incident light intensity, whereas the intensity of Raman scattering light is lower, approximately 10^{-6}–10^{-3} of the incident light intensity.[25] Due to the extremely weak Raman spectral signal, it was greatly limited in practical applications at that time. In 1974, Fleischmann *et al.*[26] found that when pyridine molecules were adsorbed on the surface of an Ag electrode, the Raman spectral intensity increased significantly, which was believed to be caused by the rough substrate, significantly improving the effective surface of the Ag electrode. In 1977, Van Duyne's[27] designed a method to measure the surface enhancement factor. They compared the SERS signal intensity of specific molecules adsorbed on a rough noble metal surface with the signal intensity of the same molecules in the solution and found that the enhancement factor can reach 10^5–10^6. The rough electrode surface generates an enhanced electric field in the electrochemical double-layer region, thereby increasing the Raman scattering cross section of the adsorbed pyridine molecules. They named this enhancement phenomenon related to rough surfaces as SERS, which effectively overcomes the shortcomings of low Raman scattering sensitivity.[28] In 1978, Moskovits[29] first explained the effect of surface plasmons on SERS enhancement on rough Ag electrodes, and predicted that similar enhancement effects may also occur in Ag and Cu colloids covered by adsorbents. In 1979, Creighton *et al.*[30] successfully verified this prediction using Ag and Au colloid. Their method expanded the research field from rough electrode surfaces to metal colloids, thereby opening up a major method for SERS research based on plasmonic nanostructures. In the past half-century, basic research and practical applications of SERS have grown steadily. In 1997, Nie, along with Emory and Kneipp,[31] independently reported the milestone breakthrough of single-molecule surface-enhanced Raman scattering (SM-SERS), pushing the detection sensitivity of SERS to the single-molecule level. Nie and others[31] achieved ultra-high enhancement of Rhodamine 6G by screening individual Ag nanoparticles with special size-dependent properties, with intrinsic enhancement factors as high as 10^{14}–10^{15}; Kneipp and others,[32] using near-infrared excitation in Ag colloidal aggregates, verified single-molecule events through poisson distribution statistics. These two studies not only experimentally confirmed for the first time the feasibility of single-molecule Raman detection, but also revealed the core contribution of "hot spots" to extreme enhancement of the electromagnetic field, laying a crucial foundation for the subsequent development of ultra-sensitive SERS analysis and single-molecule spectroscopy. In the 21st century, with the advancement of photocatalytic materials and smart-responsive materials, renewable SERS substrates have gradually become a research hotspot. In the late 2000s, semiconductor–precious metal composite substrates such as TiO_2/Ag and ZnO/Ag were demonstrated to degrade adsorbed target molecules through photogenic charge transfer under ultraviolet or visible light irradiation, achieving self-cleaning and regeneration of the substrate surface. Since the 2010s, intelligent substrates based on stimulus-responsive polymers—such as those exhibiting thermal or pH responsiveness—have further expanded renewable strategies, enabling controlled capture and release of target molecules through reversible changes in environmental conditions. The development of these renewable substrates not only reduces the cost per detection but also enhances the repeatability and long-term stability of SERS detection, providing crucial support for the application of SERS technology in practical monitoring scenarios such as antibiotic residue detection.

In recent years, SERS technology has been gradually applied to biomedical systems,[33–35] nanomaterials,[36] food safety,[37] environmental protection,[38] and other related fields because of its unique advantages, such as single-molecule sensitivity, photobleaching resistance, and multi-component detection potential. Taking the detection of antibiotic residues as an example, SERS technology can significantly enhance the Raman scattering signal of molecules by adsorbing the molecules to be tested on the surface of metal or semiconductor substrates with special structures to detect target molecules at extremely low concentrations. This technology not only provides abundant molecular structure information and realizes the specific recognition of antibiotics, but also has the advantages of simple operation, fast detection speed, and portability, which are very suitable for on-site rapid detection and real-time monitoring. Although SERS technology has shown great potential in the field of antibiotic detection, its practical application still faces many challenges, such as unclear substrate–analyte interaction mechanisms, difficult suppression of complex matrix interference, and lack of standardization, which need to be further studied and optimized (Fig. 1).

This review aims to systematically elaborate on the research progress of SERS technology in the detection of antibiotic residues in food and the environment, discuss its enhancement mechanism, substrate design innovation strategy, and practical application cases, and analyze the bottleneck and breakthrough

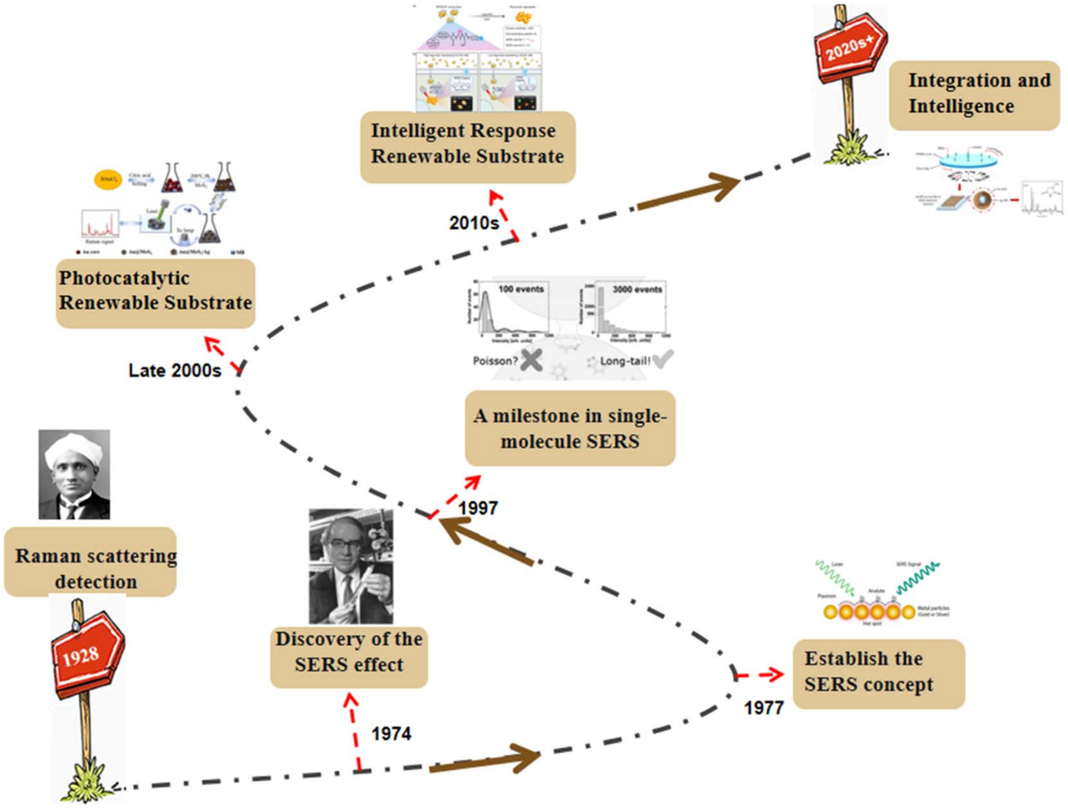

Fig. 1 Timeline of SERS technology development,[39] (Copyright 2024 by Jun Yi, is licensed under CC BY 4.0).

path in the process of technology transformation to provide useful references and enlightenment for future research and development.

2. The mechanism and signal enhancement strategy of SERS detection of antibiotics

Compared with conventional Raman spectroscopy, SERS technology has the ability to obtain information that is difficult to obtain by conventional Raman spectroscopy owing to its high-sensitivity signal. Although the SERS effect has been studied in recent decades, its mechanism remains controversial. The selected materials of the substrate, surface morphology of the sample, structural characteristics of the electrons, and interaction of light are all factors that affect the SERS effect.[40] At present, the electromagnetic enhancement mechanism (EM) and chemical enhancement mechanism (CM) are the two mechanisms recognized by scholars. Under different systems, there are often different enhancement mechanisms, so the existing enhancement effects cannot be explained by a single enhancement mechanism.

2.1 Theoretical basis of SERS enhancement mechanism

2.1.1 EM of SERS. In the vast majority of SERS processes, electromagnetic field enhancement plays a major role, mainly due to surface plasmon resonance. The mechanism of electromagnetic field enhancement was first proposed by Van duyne *et al.*, aiming to reveal the SERS enhancement of metal surface plasmon resonance in molecules.[41] Most Raman-enhanced substrates are prepared using noble metal nanomaterials because of the presence of free-moving electrons on these metal surfaces. These electrons can produce electron groups that propagate along the metal surface when interacting with photons, which is called surface plasmons.[42] When the electromagnetic wave acts on the plasma and the frequency of the two is consistent, resonance occurs, that is, Surface plasmon resonance. Surface plasmon resonance is typically divided into propagating plasmons and localized surface plasmon resonances. Propagating surface plasmons usually appear on the surface of smooth metal films. When the incident light interacts with the surface of nanoscale precious metals, the electron cloud in the metal nanoparticles will oscillate collectively, but this oscillation can only occur near the nanoparticles. The main contribution of the SERS effect is the local surface plasmon resonance. In simple terms, when the frequency of the incident light is the same as the frequency of the collective motion of these electrons, localized surface plasmon resonances (LSPR) will be generated, resulting in a sharp increase in the intensity of the local electromagnetic field, which greatly increases the probability of Raman scattering of molecules, resulting in a sharp increase in SERS signals. The theoretical calculation of the electromagnetic enhancement effect can reach 10^{10}–10^{11} (Fig. 2). In the actual process, the SERS enhancement effect is often affected by the shape and size of the SERS substrate (nanomaterial), wavelength of the excitation light, and the distance between the target molecule and the surface of the nanomaterial.[41] The enhancement factor was approximately proportional to the fourth power of the local electromagnetic field intensity.[43] With further research, researchers have found that a large number of surface atoms are gathered at the tip structure position of the metal nanosurface with a large curvature, and more surface electrons are gathered near these atoms. When the metal nanoparticles are close to each other to a certain distance, the local electric field at the gap of the nanoparticles will also be enhanced, thus forming a strong localized electromagnetic field generated by the resonant coupling of plasmons, which is called the "hot spot" effect.[44–46] In 1997, the milestone breakthrough of single-molecule SERS detection directly confirmed the decisive role of "hot spots" in the extreme enhancement of the electromagnetic field. Nie *et al.*[31] by screening individual Ag nanoparticles with specific size-dependent characteristics, found that when Rhodamine 6G molecules adsorbed at the tips or corners of these particles, the intrinsic enhancement factor reached 10^{14}–10^{15}, far exceeding the conventional ensemble average enhancement values. Kneipp *et al.*[32] on the other hand, achieved single-molecule detection in Ag colloid aggregates using near-infrared excitation, and pointed out that less than 1% of the aggregates exhibited single-molecule activity. These highly active sites are precisely the 'hot spots' formed in the gaps between nanoparticles. Subsequent theoretical calculations show that in structures such as Ag nanoparticle dimers, the localized electromagnetic field enhancement at the gaps can reach over 10^9, and the enhancement factor is inversely proportional to the fourth power of the gap distance.[44,47] This extreme electromagnetic field distribution also explains why the SERS signal mainly comes from a very small number of molecules in the 'hot spots' on the substrate surface—about 1% of the molecules contribute more than 70% of the total signal intensity. Therefore, "hot spots" are not only the core carriers of the electromagnetic enhancement mechanism but also the fundamental physical basis for achieving ultra-sensitive single-molecule detection using SERS technology. This discovery further enhances the SERS signal and makes single-molecule detection possible. The mechanism of electromagnetic field enhancement is based on the contact between molecules and nanoparticles, which can greatly enhance the SERS signal of the target molecules.[48] In other words, the distance between the molecule and nanometal surface determines the strength of the molecular SERS signal.[49,50] When the distance between the molecule and nanometal surface is smaller, the local electromagnetic field intensity at the position of the molecule is stronger, and the obtained SERS signal is stronger. Because the electromagnetic field enhancement mechanism is limited to the region near the surface of the nanoparticle, the local electromagnetic field intensity in this region decays exponentially with the increase of the distance between the molecule and the surface of the nanoparticle.[51,52]

2.1.2 CM of SERS. CM is mainly due to the interaction between the molecule and the metal surface, which changes the electronic state of the molecule and enhances the Raman scattering signal. Specifically, when the molecule is adsorbed on the metal surface, charge transfer (CT) and redistribution occur between the free electrons of the metal and the electron cloud of the molecule, which changes the polarizability of some vibration modes of the molecule, thereby enhancing the Raman scattering intensity corresponding to these vibration modes[53] (Fig. 2). CM is one of the important foundations of SERS sensors for the detection of antibiotic residues in food and environment. CT plays a key role in this mechanism. The energy level matching between the antibiotic molecule and the substrate directly affects the efficiency of the CT, which in turn affects the intensity of the SERS signal.[54] In the tetracycline-Ag system,[55] when the energy levels of the tetracycline molecule and Ag substrate are well matched, the charge can be effectively transferred between the two, thereby significantly enhancing the Raman signal. This CT process not only enhances the signal

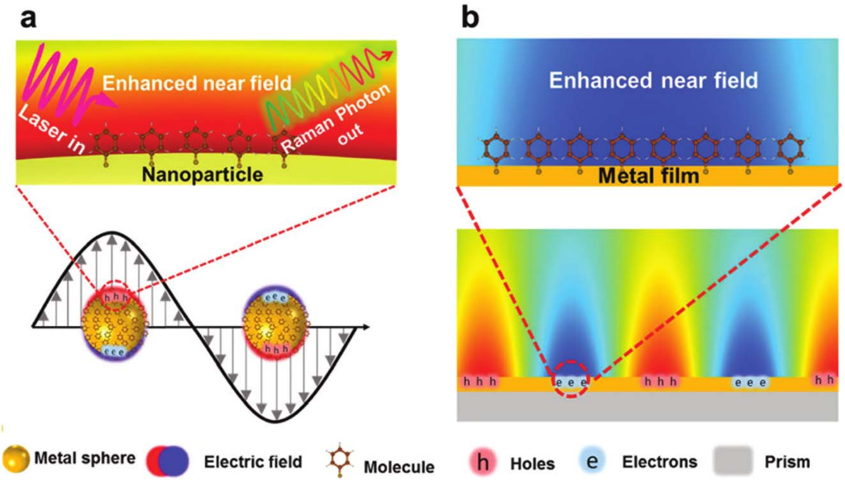

Fig. 2 The schematic diagram of local plasma (a) and propagating surface plasma (b) (this figure has been adapted/reproduced from ref. 41 of the American Chemical Society, copyright 2008).

intensity, but also provides specific information for the detection of antibiotic molecules. The effect of the molecular orientation on the SERS signal intensity cannot be ignored. In the detection of sulfonamides,[56] when they are vertically adsorbed on the substrate surface by π–π stacking, the SERS signal intensity can be enhanced by 10 times. This phenomenon can be explained using density functional theory (DFT) simulations. DFT simulations show that the molecular orbital of the sulfonamide drug molecule is more matched with the electron cloud distribution on the substrate surface when it is vertically adsorbed, thus promoting the synergistic effect of charge transfer and electromagnetic field enhancement, resulting in a significant enhancement of the SERS signal. The optimization of molecular orientation improves the detection sensitivity, provides theoretical guidance for the design of high-performance SERS substrates. Substrate design is key to achieving efficient SERS detection. To enhance the SERS signal, researchers usually design a substrate structure with a high specific surface area and rich "hot spots".[57] Nanomaterials such as Au NPs, Ag NPs and their composites are widely used in the preparation of SERS substrates. These nanomaterials have good plasmon resonance effect, can further improve their interaction with antibiotic molecules through surface modification. In addition, the design of the multistage cavity structure substrate provides a new idea for SERS detection. The Ag/ZnO/PDMS multistage cavity structure substrate significantly improves the intensity and stability of the SERS signal by combining the plasmon and optical resonance effects of the cavity structure.[58] It is worth noting that the electromagnetic field enhancement is a long-range effect limited to the evanescent field, which decays exponentially with the increase of the distance between the probe molecule and the SERS substrate, while the chemical enhancement is a short-range effect on the scale, and there is a direct interaction between the probe molecule and the substrate (Fig. 3).[59]

2.1.3 Synergistic effect of EM and CM. The enhancement mechanism of SERS technology mainly includes EM and CM. There is a synergistic effect between the two mechanisms, which works together to achieve a significant enhancement of the Raman signals. The design of a bifunctional substrate can make full use of the synergistic effects of electromagnetic field enhancement and chemical enhancement to achieve a higher SERS signal enhancement factor (EF).[60] Li *et al.*[61] mixed positively charged Ag NPs with negatively charged $Ti_3C_2T_x$ by electrostatic self-assembly, creating many uniform "hot spots" for the substrate. Owing to the high affinity between the tested molecule and $Ti_3C_2T_x$, the charge transfer between the molecules was promoted, resulting in a significantly enhanced effect. After the successful preparation of $Ti_3C_2T_x$/Ag NPs substrate, the SERS activity was studied using R6G dye molecules. According to the results, the substrate can achieve an EF of 3.8×10^8. In addition, it has been proved that the coupling effect between EM and CM is the main reason for the excellent performance of $Ti_3C_2T_x$/Ag NPs composite substrate (Fig. 4). This synergistic effect improves the sensitivity of the SERS sensor, provides the possibility for its application in complex samples, such as the detection of antibiotic residues in food and environment. In practical applications, the design of bifunctional substrates must comprehensively consider factors such as material selection, structural optimization, and surface functionalization to achieve the best enhancement effect and selectivity. Zhai *et al.*[62] further expanded the design concept of composite substrates. They prepared regenerated 3D ZnO/Ag@Au substrates and triggered strong electromagnetic enhancement effects by adjusting the electron distribution of the metal and semiconductor metal oxides. The synergistic physical and CM were verified using density functional theory and finite-difference time-domain simulations. This systematic study from theory to experiment increases the EF to 1.48×10^9, further reducing the detection limit, which provides more powerful technical support for the application of SERS sensors in the detection of actual complex samples. The transformation from $Ti_3C_2T_x$/Ag NPs to ZnO/Ag@Au reflects the innovation and optimization of researchers in material selection and structural design, and further promotes the performance of SERS sensors. However, in addition to this design idea based on the metal–semiconductor composite structure, the Ag@MoS_2 core–shell structure is a typical bifunctional substrate. The outer layer of MoS_2 can form a heterostructure with Ag to achieve effective CT and redistribution, and enhance the polarization effect of the molecule. Simultaneously, the Ag core provides a strong local electromagnetic field, and the synergistic effect of the two increases the EF value by two orders of magnitude.[63] The EF value in this study has increased slightly, and other researchers have increased the EF value to 10^8. These studies enrich the design ideas of SERS substrates and provide a valuable reference for the development of high-performance SERS sensors.

2.1.4 DFT calculations on adsorption orientation and SERS intensity. Density functional theory (DFT) calculations are an important theoretical tool for revealing the adsorption behavior of antibiotic molecules on SERS substrate surfaces and the essence of signal enhancement. By constructing metal clusters (such as Ag10–Ag20) or periodic slab models, DFT can simulate adsorption configurations of antibiotic molecules on the substrate surface in different orientations (horizontal or vertical), and further calculate the system's geometrical structure, vibrational frequencies, polarizability, and interfacial charge transfer characteristics. For the calculation of polarizability, DFT can obtain the molecule's static polarizability tensor (α) and its first derivative with respect to normal coordinates ($\partial\alpha/\partial Q$), while the Raman scattering intensity is proportional to $|\partial\alpha/\partial Q|^2$.[64] Research shows that when antibiotic molecules are vertically adsorbed, the change in polarizability along their long axis is often more significant, resulting in the corresponding vibrational modes having a larger Raman scattering cross-section, thereby exhibiting stronger signals in SERS spectra. In contrast, during horizontal adsorption, the contact area between the molecule and the metal surface is smaller, the derivative of polarizability decreases, and the signal intensity is usually reduced by about 50%.[63] For the calculation of charge transfer, DFT can quantitatively describe the amount of electron transfer between antibiotic molecules and the substrate through methods such as differential charge density, Bader charge analysis, or Hirshfeld charge population.[65] At the same

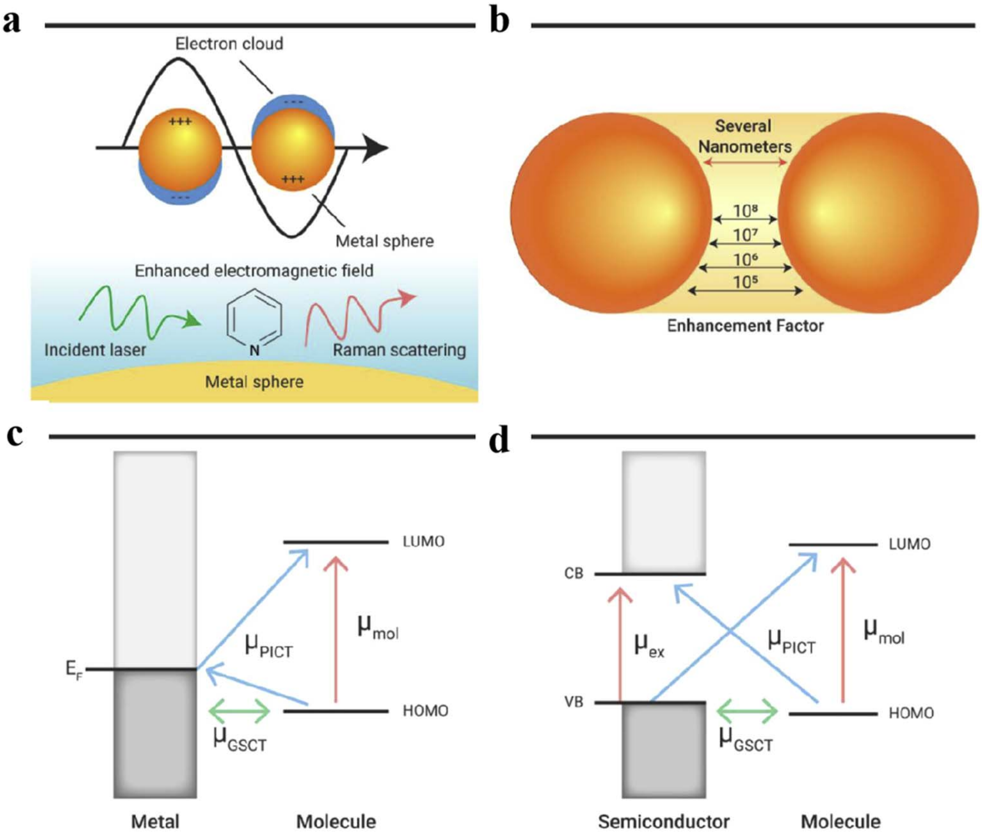

Fig. 3 (a) Based on the SERS electromagnetic enhancement of plasma nanospheres, (b) the "hot spot" in the gap between adjacent particles and the corresponding change of SERS enhancement factor with relative position, (c) the comparison of charge transfer transition in metal-molecular system and (d) semiconductor molecular system (this figure has been adapted/reproduced from ref. 53 from PUBLISHER *Chemical Mechanism of SERS*, copyright 2024).

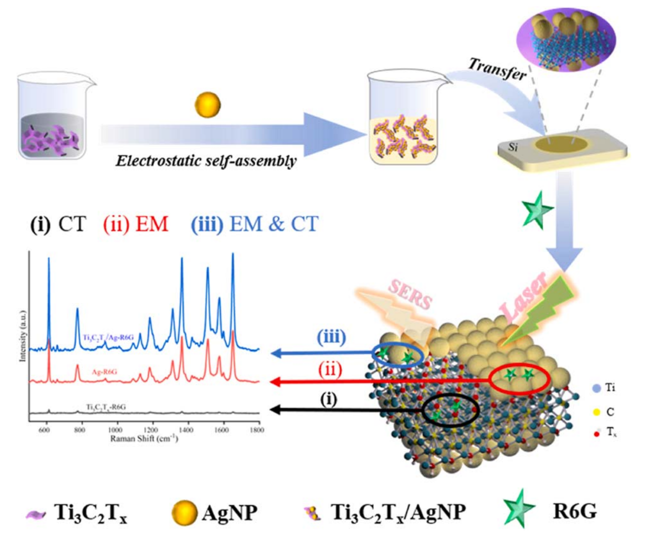

Fig. 4 Enhancement mechanism of $Ti_3C_2T_x$/AgNPs composite substrate, this figure has been adapted/reproduced from ref. 61 from PUBLISHER *Journal of the Analytica Chimica Acta*, copyright 2024.

time, by analyzing the relative positions of the molecule's highest occupied molecular orbital (HOMO) and the metal's Fermi level, the efficiency of charge transfer can be evaluated: when the energy levels match well, electrons induced by light excitation transfer from the metal to the molecule's unoccupied orbitals or the reverse transfer occurs, significantly enhancing the Raman scattering of specific vibrational modes.[49] In the study of the tetracycline-Ag system and sulfonamide drugs, DFT simulations confirmed that when adsorbed vertically, the molecular orbitals have better overlap with the substrate's electron cloud distribution, thereby promoting the synergistic effect of charge transfer and electromagnetic field enhancement.[66,67]

A research study published in 2017 by the team led by Professor Huang Qing at the Hefei Institutes of Physical Science, Chinese Academy of Sciences was published in The *Journal of Physical Chemistry C*.[68] Using adenine as the model molecule, the study proposed a novel methodology combining density functional theory calculations with isotopic labeling SERS experiments. The team's specific work included: first, conducting DFT calculations at the B3LYP/6-311+G(d,p) theoretical level to simulate the geometric optimization, adsorption energy, and theoretical Raman spectra of adenine in different adsorption configurations on silver and gold surfaces; second, preparing fully 15N-labeled adenine and collecting its SERS experimental spectra on silver and gold nanoparticles. By comparing the peak positions, relative intensities, and isotopic shifts between theoretical simulations and experimental measurements, the research team confirmed that adenine adopts the same adsorption configuration on both silver and gold surfaces—specifically, N_7H adenine interacts with Ag_4^+/Au_4^+ clusters through the N_3 and N_9 sites. This methodology can also be extended to antibiotic systems—by preparing ^{15}N-or ^{2}H-labeled antibiotic molecules, the characteristic peaks in the SERS spectrum can be accurately identified, and the specific adsorption sites and orientations of antibiotics on the substrate surface can be determined. Notably, in addition to the work of Huang Qing's team, the teams led by Takeshi Tanaka and Yukio Ozaki at Kansai Gakuin University in Japan pioneered the "SERS spectroscopy + DFT calculation" research paradigm as early as 2003.[69] Using *o*-, *m*-, and *p*-nitroanilines as model systems, the team employed DFT methods to calculate the electrostatic properties, vibration frequencies, and Raman scattering intensities of these molecules. Combined with SERS experiments, they discovered that although *o*-nitroaniline and *p*-nitroaniline share the same structural formula, differences in substituent positions resulted in distinct molecular dipole moments and polarizabilities, leading to different adsorption orientations on metal surfaces. This work establishes a methodological foundation for subsequent studies employing the DFT-SERS integrated strategy to investigate the adsorption behavior of drug molecules, including antibiotics. Furthermore, in 2023, Maurizio Muniz-Miranda from the University of Modena-Rajao Emilia in Italy and the University of Florence, along with his collaborators, published a review in the journal Molecules that systematically summarized the advancements of DFT methods in SERS spectral simulation.[70] The review focuses on how DFT calculations can elucidate the anchoring mechanisms between adsorbed molecules and metal substrates, bonding strengths, as well as adsorption-induced structural and electronic property changes. DFT calculations provide crucial theoretical guidance for optimizing SERS substrate design and enhancing the sensitivity and selectivity of antibiotic detection. Through DFT simulations, the optimal adsorption orientations of various antibiotic molecules on specific substrates can be predicted, enabling researchers to develop targeted surface functionalization strategies for efficient capture and signal enhancement of target antibiotics.

2.2 SERS response characteristics of antibiotic molecules

SERS technology has shown great potential for the detection of antibiotic residues in food and the environment because of its ultra-high sensitivity and molecular fingerprint recognition ability. Antibiotic molecules exhibit unique response characteristics in SERS spectra, mainly due to their specific functional groups and molecular structures. The β-lactam ring of β-lactam antibiotics such as penicillin produces specific fingerprint peaks in the Raman spectrum, which can be used as a basis for identification and quantitative detection.[71] Similarly, the aminoglycoside structure of aminoglycoside antibiotics (such as streptomycin) also produces obvious vibration modes at specific Raman shifts, which are characterized by characteristic peaks in the SERS spectrum.[72]

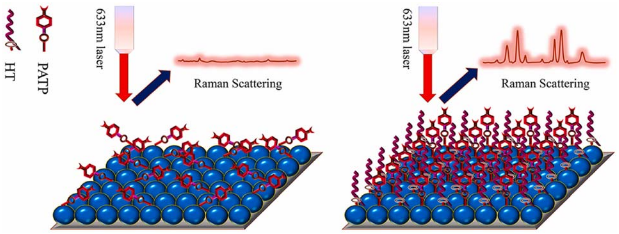

Fig. 5 Comparison of SERS signal intensity of fluoroquinolone antibiotics in horizontal adsorption and vertical adsorption (this figure has been adapted/reproduced from ref. 75 from PUBLISHER *Talanta*, copyright 2019).

The orientation and adsorption configuration of the molecules significantly affected the SERS signal intensity. Studies have shown that the adsorption mode of molecules on the substrate surface directly affects the intensity and stability of Raman signals.[73,74] The SERS signal intensity of fluoroquinolone antibiotics in horizontal adsorption is about 50% lower than that in vertical adsorption. This difference is mainly due to the difference between the electromagnetic field enhancement effect and the chemical enhancement effect between the molecule and substrate. During horizontal adsorption, the contact area between the molecule and substrate is small, resulting in a weakening of the electromagnetic field enhancement effect. In the case of vertical adsorption, the contact area between the molecule and substrate is larger, and the electromagnetic field enhancement effect is stronger, resulting in a stronger SERS signal[75] (Fig. 5).

3. Innovative strategies for SERS substrate design

SERS substrate is an indispensable core component of the SERS technology. It is a special substrate material that can significantly enhance the Raman scattering signal of molecules adsorbed on its surface or adjacent areas, so that the original weak Raman signal can be detected and analyzed. The design of the SERS substrate is key to achieving highly sensitive detection. In recent years, researchers have optimized the performance of SERS substrates through a variety of innovative strategies.

3.1 Selection of SERS substrate materials

The activity of SERS substrate affects its sensitivity and detection limit in practical detection. Therefore, the preparation of SERS substrates with high activity is key for the application of SERS detection. Based on SERS enhancement theory, the SERS detection process involves the coupling effect of three complex influencing factors between photons, molecules, and prepared nanostructures. In the process, more SERS "hot spots" can be created by adjusting the structure of the substrate to enhance the interaction between the molecule to be tested and the prepared SERS substrate, thereby improving the detection sensitivity. SERS substrates are mainly composed of noble metal nano-materials, noble metal/semiconductor materials, and composite/flexible substrates. In the study of substrate material preparation, the substrate with excellent enhancement performance is obtained by adjusting the size, shape, spacing between particles and compounding of materials.[76]

3.1.1 Noble metal nanostructures. Traditional noble metal materials including Au, Ag, Cu, *etc.*, as commonly used plasma nanostructures, are commonly used SERS substrate materials. The localized surface plasmons of noble metal materials such as Au, Ag and Cu are more easily excited. These materials also exhibit unique light absorption characteristics. By changing the nanoradius, morphology of nanomaterials, and other conditions, the resonance frequency can be changed to achieve selective absorption and scattering of the incident light.[77] Nguyen *et al.*[78] established the use of Au NPs for the visual detection and high-sensitivity quantification of meropenem in drug and human plasma samples. This method is based on the aggregation caused by the interaction between citrate-capped Au NPs and meropenem, resulting in changes in the surface plasmon resonance. The trace amount of meropenem can be detected by visually observing the change in the color of the Au NPs solution from red to blue, corresponding to the movement of the maximum absorbance in the UV-vis spectrum from 520 nm to 660 nm. Meropenem can be quantified by the linear relationship between the light absorption ratio A660/A520 and the logarithm of meropenem concentration. The method has high recovery was 97.6–101.5%, RSD < 4.5%, and the LOD was 0.06 mg L^{-1}, which further reflects the importance of precious metal materials in analytical chemistry. The three noble metals, Au, Ag and Cu, have the properties of visible and near-infrared wavelengths, and the wavelength range of Raman test is fully covered. These properties also improve the SERS enhancement effect of noble metal materials.[79] The detection signal intensity of the SERS substrate can be maximized by changing the structure of the noble-metal substrate and optimizing the particle size.[80]

Neng *et al.*[81] constructed a MIPs-SERS sensor based on Ag NPs film for selective detection of enrofloxacin in food. A layer of Ag NPs with the best SERS effect was synthesized on the surface of copper rod by *in situ* reduction as the reinforcing material, and then the targeted MIPs were prepared by intrinsic polymerization, which contained the template molecules encapsulated on the surface of Ag nanoparticle film (Ag NPs-MIPs). The results showed that Ag NPs-MIPs could specifically recognize enrofloxacin from complex environments with the LOD was 0.25 ng mL^{-1}. However, the cost of preparing small-sized precious metals increases, and when the particle size of precious metals is small, Au NPs and Ag NPs will agglomerate, affecting the uniformity and repeatability of the substrate, which will limit the application of SERS detection technology in actual detection.[82] Based on the morphology of the SERS substrate of noble metal materials, various changes can be produced by the use of surfactants, and noble metal nanoparticles with different morphologies are prepared: nanorods, nanowires, nanospheres, nanostars, *etc.*[83] For example, Diego M. Solis *et al.*[84] studied the enhancement effect of noble metal nanoparticles with different morphologies through theoretical calculations. It is concluded that the structure with simple morphology in non-dense arrangement has better enhancement effect, but in the single arrangement structure, the structure of nanostars shows better enhancement effect (Fig. 6). Riswana Barveen *et al.*[85] photochemically synthesized Au nanostars (Au NSs) on PMMA film by ethanol as a flexible SERS substrate for *in situ* detection of antibiotics. The proposed flexible Au NSs/PMMA SERS substrate is characterized by SERS detection of two antibiotics ciprofloxacin and chloramphenicol. Excellent detection performance: including high sensitivity, high EF was 2.03×10^9, the LOD was 3.41×10^{-11} M, excellent multiple detection ability, good mechanical stability, excellent uniformity and reproducibility, RSD < 7.32%. This study fully proves that the rational design of the morphology and preparation methods of noble metal nanoparticles can overcome the challenges in practical applications and achieve high-performance SERS detection, which provides an important reference for the future development of SERS technology.

3.1.2 Precious metal–semiconductor materials composites. The so-called composite substrate refers to the substrate material prepared by compounding two or more materials. Noble metal nanomaterials such as Au and Ag have surface plasmon resonance (SPR) effect, which can excite strong local electromagnetic fields on their surfaces, thereby significantly enhancing SERS signals. Semiconductor materials can also

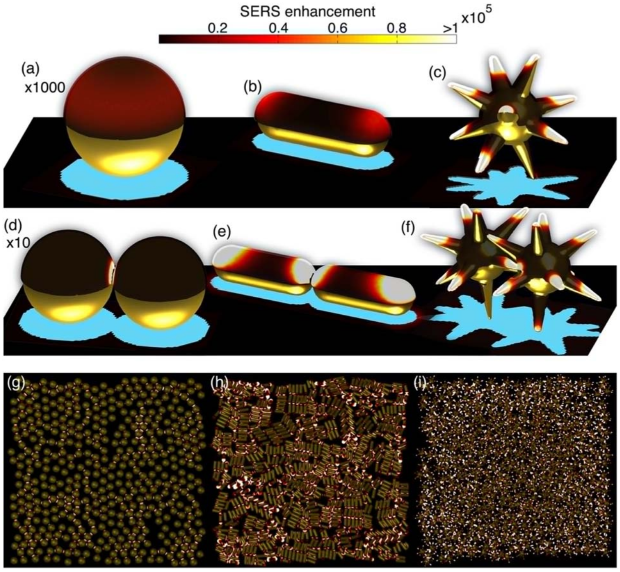

Fig. 6 Enhancement effect of noble metal nanoparticles with different morphologies,[84] near-field analysis of SERS enhancement in isolated particles, dimers, and monolayers of GNPs, GNRs, and GNSs. (a–c) Spatial distribution of the SERS enhancement on a molecular skin deposited 1 nm away from the metal surface for individual nanoparticles simulated at the respective incident light wavelengths to yield maximum enhancement for zero Raman shift (525, 615, and 875 nm for GNPs, GNRs, and GNSs). (d–f) Same as (a–c) for dimers (1 nm minimum gap distance), with maxima now shifted to 570, 690, and 890 nm, respectively. (g–i) Same as (d–f) for planar monolayers (437 GNPs, 740 GNRs, and 504 GNSs, respectively, randomly distributed on a $1.2 \times 1.2\ \mu m^2$ area) calculated at the new peak wavelengths (620, 700, and 980 nm, respectively). (Copyright 2017 by Diego M. Solis, is licensed under CC BY 4.0).

produce similar effects under certain conditions. The surface plasmon resonance effect of semiconductors can be excited by introducing oxygen vacancies, defects, *etc.* When the semiconductor is combined with the noble metal, the synergistic effect between the two can further enhance the intensity of the local electromagnetic field, thereby increasing the intensity of the SERS signal. At the same time, by compounding different materials, it can adapt to the application of the substrate in different fields and improve the value in practical applications. The introduction of noble metal materials also improves the defects of the existing enhancement ability.[86,87] Composite materials have good biocompatibility, excellent performance in stability and detection sensitivity, and have better application prospects in the field of analysis and detection. The combination of semiconductor materials and precious metals has promoted the theoretical research and application research of SERS detection technology.[88] Zhao *et al.*[89] studied metals and semiconductors (TiO_2, ZnO, CuO, *etc.*), and adjusted the metal–semiconductor induced CT behavior heterojunction. In the noble metal–semiconductor composite structure, the noble metal exhibits a strong SPR effect in the visible region, which can expand the range of light absorption. The Fermi level of noble metals is generally lower than that of semiconductors, which promotes the separation of photogenerated electrons and holes, effectively improves the efficiency of intermetal CT, and obtains a substrate material with better SERS activity. Yang *et al.*[90,91] studied the SERS of the prepared Ag-TiO_2 and Au-ZnO noble metal and semiconductor composite substrates, and showed that the composite SERS substrate had a better enhancement effect (Fig. 7). The enhancement reason is mainly reflected in the surface plasmon resonance of noble metals (Ag, Au). In the case of light excitation, the electromagnetic field intensity is improved to a certain extent, thereby enhancing the Raman scattering intensity of the probe molecule. The charge transfer (chemical enhancement) between the semiconductor material and the probe molecule is enhanced, and the Raman signal intensity is further improved.

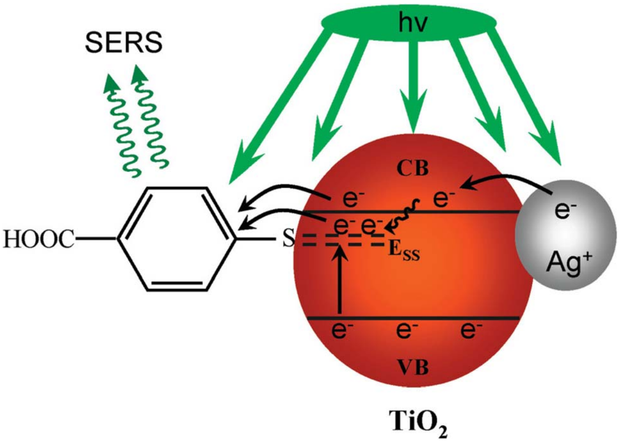

Fig. 7 SERS enhancement mechanism model of noble metal–semiconductor composite structure (this figure has been adapted/reproduced from ref. 90 from PUBLISHER *Journal of Physical Chemistry C*, copyright 2009).

3.1.3 **Composite flexible substrate.** The composite flexible substrate is a new type of SERS substrate, which is made of flexible materials and has excellent flexibility. This substrate is usually supported by flexible polymer materials, and the Raman signal is significantly enhanced by loading metal nanoparticles or other SERS-active materials on its surface. In terms of antibiotic detection, the advantages of the composite flexible substrate are mainly reflected in its good flexibility, which enables it to adapt to various complex detection environments and sample forms, such as curved pipes and irregular surfaces. Secondly, the composite flexible substrate can be combined with a variety of detection technologies, such as fluorescence detection, electrochemical detection, *etc.*, to achieve multimode collaborative detection and improve the sensitivity and accuracy of detection. In addition, the composite flexible substrate can also achieve selective recognition and detection of specific antibiotics through surface modification and functionalization, thereby reducing interference and misjudgment in the detection process. The composite flexible substrate has broad application prospects in the field of antibiotic detection. With the continuous development of materials science, nanotechnology and analytical chemistry, the performance and function of composite flexible substrates will be further improved and expanded, providing more effective methods and means for solving practical detection problems.

Luo *et al.*[92] prepared environmentally friendly chitosan (CS)/carbon nitride (CN) with three-dimensional porous structure by freeze-drying method, and then prepared a new bifunctional flexible substrate (CS/CN/Ag) by anchoring small-sized Ag NPs (6–12 nm) on CS/CN. Importantly, the CS/CN/Ag substrate showed a high adsorption capacity (~83.06%) for sulfamethoxazole (SMX) solution within 20 min, with a LOD was 7.46×10^{-9} M and an enhancement coefficient of 3.3×10^5. In addition, the CS/CN/Ag substrate showed high selectivity for SERS detection of sulfonamides, and also showed excellent SERS response to SMX in hospital wastewater samples. The photocatalytic degradation efficiency of SMX can reach 99.22% within 20 min after irradiation, and CS/CN/Ag still maintains excellent photocatalytic performance after 6 cyclesn (Fig. 8a). Han *et al.*[93] further expanded the design idea of composite materials, and developed a new type of PI/TiO_2/Ag organic–inorganic ternary flexible microfibers based on semiconductor titanium dioxide (TiO_2), noble metal Ag and conjugated polymer polyimide (PI). The photocatalytic performance of PI/TiO_2/Ag flexible microfibers containing different amounts of Ag quantum dots (QDs) was investigated by photocatalytic degradation of tetracycline in aqueous solution under sunlight. This shows that in the design of composite materials, the efficient degradation of specific pollutants can be achieved by reasonably selecting and matching materials with different functions (Fig. 8b). It also provides a new direction for the performance optimization of composite materials in subsequent research, that is, by adjusting the composition and structure of materials to improve its application effect in environmental governance. Fan *et al.*[94] returned their research focus to the development of high-sensitivity detection technology based on composite materials. They

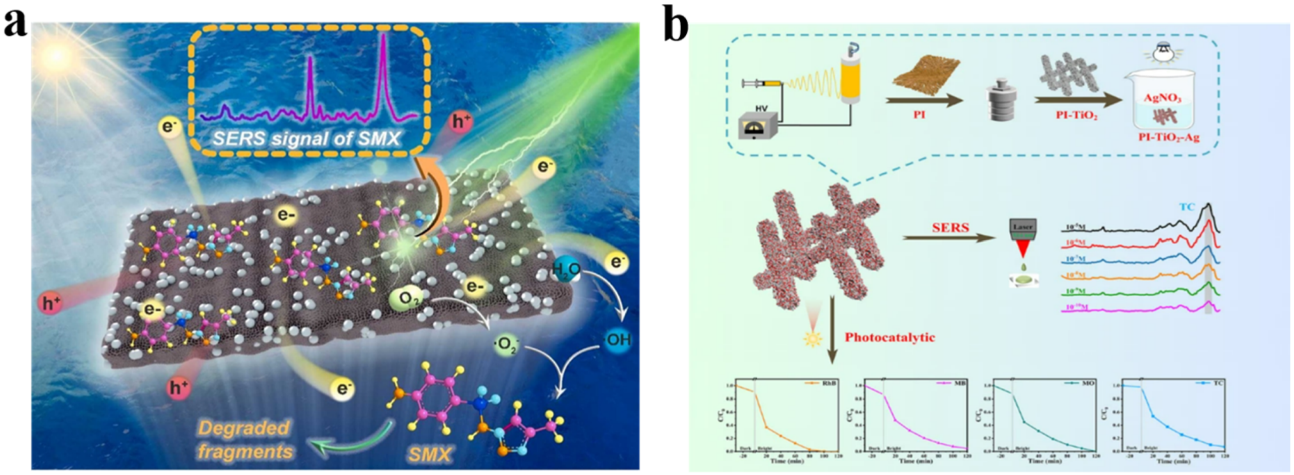

Fig. 8 (a) The principle of SMX adsorption on CS/CN/Ag substrate, (this figure has been reproduced from ref. 94 from PUBLISHER *Journal of Hazardous Materials*, copyright 2023,[92] (b) the sensitive detection of antibiotics by PI/TiO_2/Ag flexible microfibers and the schematic diagram of efficient photocatalytic degradation,[93] (Copyright 2024 by Donglai Han, is licensed under CC BY 4.0).

prepared a core–shell nanofiber membrane with a "net bead" morphology by electrospinning technology, and coated an ultrathin Ag layer on it to prepare a SERS nanosensor. The design of this sensor makes full use of the optical properties of nanostructures and realizes the low concentration detection of sulfamethoxazole. This indicates that in the application of composite materials, their photocatalytic performance be used for pollutant degradation, high-performance detection devices can be developed by optimizing the structure and composition. It reflects the connection and expansion of composite materials in the two fields of environmental governance and analysis detection, while realizing the degradation of pollutants, it also provides a new technical means for the detection of pollutants, and further promotes the comprehensive application of composite materials in the environmental field.

3.1.4 Carbon-based and 2D material hybrid substrates. Carbon-based materials (such as graphene, graphene oxide, carbon nanotubes, carbon dots, *etc.*) and two-dimensional layered materials (such as transition metal sulfides, MXene, *etc.*) have become a research "hots pot" in recent years for constructing high-performance SERS composite substrates due to their unique physicochemical properties. This type of material itself has an extremely high specific surface area, excellent chemical stability, tunable electronic structure, and abundant surface functional groups, which can effectively enrich antibiotic molecules and generate a chemically enhanced effect through a charge transfer mechanism.[95] When combined with noble metal nanoparticles, carbon-based/two-dimensional materials can not only serve as a supporting framework to regulate the distribution and spacing of metal nanoparticles, thereby creating more uniform "hot spots", but also produce a synergistic enhancement effect with noble metals, significantly improving the sensitivity and selectivity of SERS detection.

Graphene and its derivatives (such as graphene oxide GO and reduced graphene oxide rGO) have atomically flat surfaces, a high π–π conjugated structure, and good electron mobility. They can effectively adsorb antibiotic molecules containing aromatic ring structures through π–π stacking interactions, while the oxygen-containing functional groups on their surfaces can form stable composite structures with metal nanoparticles. Qu *et al.*[96] prepared Ag NPs/CNT intercalated GO composite films, using the layered structure of GO to efficiently enrich tetracycline and ampicillin, achieving sensitive SERS detection of the two antibiotics, with detection limits of 1.5 nM and 3.2 nM, respectively, and the substrate exhibited long-term stability of 70 days. Nguyen *et al.*[97] developed a nanocomposite based on GO and Au NPs for the detection of kanamycin in microfluidic systems. This substrate effectively suppresses the signal fluctuation issue of traditional SERS substrates, has a wide detection range (1–100 mM), and is reusable. In addition, carbon nanotubes (CNTs), as one-dimensional carbon-based materials, have a high aspect ratio and excellent conductivity. When combined with Ag NPs, they can form a three-dimensional network structure, increasing the density of hot spots and molecular adsorption sites.[98]

MXenes (such as $Ti_3C_2T_x$) are an emerging class of two-dimensional transition metal carbides/nitrides, possessing metallic-level conductivity, hydrophilic surfaces, and abundant terminal functional groups (such as –O, –OH, –F).[99] These characteristics enable them not only to serve as excellent SERS substrate support materials but also to generate significant chemical enhancement through interfacial charge transfer. Li *et al.*[100] Prepared a $Ti_3C_2T_x$/Ag NPs two-dimensional SERS substrate by electrostatically self-assembling positively charged Ag NPs with negatively charged $Ti_3C_2T_x$ nanosheets. This substrate formed a large number of uniform "hot spots", and due to the high affinity between $Ti_3C_2T_x$ and the target molecules facilitating intermolecular charge transfer, the enhancement factor for R6G molecules reached 3.8×10^8.[61] In terms of antibiotic detection, this substrate exhibits excellent sensitivity and reproducibility for drugs such as enrofloxacin. Such MXene/precious metal composite substrates fully combine the synergistic effects of electromagnetic enhancement and chemical enhancement, providing a new strategy for the highly sensitive detection of antibiotic residues in complex matrices.

Transition metal sulfides (TMDs), represented by MoS_2 and WS_2, have tunable band gaps and strong light–matter interactions. When combined with precious metal nanoparticles, TMDs can not only promote photogenerated charge separation and interfacial charge transfer by forming heterojunctions, but also utilize their edge defects and sulfur vacancies to adsorb antibiotic molecules. Chen *et al.*[8] Designed a Ag@MoS_2 core–shell structure, in which the outer MoS_2 forms a heterojunction with the Ag core, achieving effective charge transfer and redistribution, enhancing the molecular polarizability; meanwhile, the Ag core provides a strong localized electromagnetic field, and the synergy of the two increases the enhancement factor by two orders of magnitude. This substrate exhibits ultra-sensitive detection capabilities for various antibiotics (such as ciprofloxacin and tetracycline).[101] In addition, the MoS_2/Ag NP nanocup structure can further capture target molecules through the confinement effect, enhancing detection stability.[102]

3.2 Functional modification strategy of SERS substrate

The SERS substrate adopts a functional modification strategy, which can significantly improve the detection sensitivity and selectivity of specific antibiotics. These modification strategies include the use of molecularly imprinted polymers (MIPs), aptamer/antibody modification, and reporter coding to enhance SERS signals and improve detection performance.

3.2.1 MIPs. MIPs are highly specific and selective materials, which can achieve efficient recognition of target molecules by simulating specific binding sites of biological recognition molecules. When modified on the SERS substrate, these recognition sites can specifically bind to the target molecule, thereby improving the selectivity of SERS detection, reducing the interference of non-specific adsorption, and making the SERS signal more accurately reflect the information of the target molecule. MIPs can specifically recognize the target antibiotics, effectively avoid the interference of other substances in complex samples, and improve the selectivity of detection. By selecting the appropriate functional monomers and template molecules, MIPs can form stable complexes with target antibiotics to achieve highly selective detection.[103] Cheng *et al.*[104] innovatively used *o*-phenylenediamine and *p*-amino-benzoic acid as bifunctional monomers to prepare MIP sensors for high-sensitivity analysis and determination of chloramphenicol (CAP). The MIP sensor has a detection range was 0.0001–125 μM and the LOD was 6.6 pM, with excellent selectivity and stability. In addition, the researchers also tried to introduce conductive nano-materials and other functional molecules, such as graphene and Au NPs, during the preparation of MIPs. The sensitivity of SERS technology has been significantly improved, and extremely low concentrations of antibiotics can be detected. MIPs have good chemical stability and thermal stability, and can maintain their recognition performance in complex environments. SERS technology combined with MIPs can achieve multiple detection and identify multiple antibiotics at the same time, which provides the possibility for the analysis of complex samples (Fig. 9). Gao *et al.*[105] combined molecularly imprinted polymers with SERS (MIPs-SERS) to develop an innovative nanobiosensor for the determination of chloramphenicol (CAP) in milk and honey products. MIP polymerization was formed by precipitation using template molecule, functional monomer (acrylamide), crosslinking agent (ethylene glycol dimethacrylate), initiator (2,2′-azobis(isobutyronitrile)) and porogen (methanol). Ag nanostructures were used as SERS active substrates for the determination of CAP in food matrices. The separation and enrichment of antibiotics plays an important role in the detection process. Researchers have introduced magnetic materials to solve the above problems. Ashley *et al.*[106] developed a new analytical method that combines sample preparation based on magnetic molecularly imprinted polymer (MMIP) with detection based on SERS for the quantitative analysis of cloxacillin in pig serum. The large loading and high selectivity of core–shell structure MMIP micro-spheres can effectively extract cloxacillin, and the magnetic sensitivity greatly simplifies the sample processing procedure. A low-cost and robust SERS substrate composed of vertical Au cap-silicon nanocolumns was fabricated and used for the detection of *o*-cloxacillin. This method has good sensitivity. The LOD was 7.8 pM, and the recovery rate was more than 80%.

3.2.2 Aptamer modification. Aptamers are a class of single-stranded DNA or RNA fragments that can specifically bind to target molecules, with high affinity and specificity. In SERS detection, the aptamer binds to the SERS substrate by electrostatic adsorption, covalent bonding and biotinstreptavidin interaction, and the aptamer acts as a recognition element to specifically bind to the target antibiotic molecule, thereby achieving targeted capture of the target antibiotic.[107] Jiang *et al.*[108] proposed a novel SERS-based aptamer sensor for the first time using 4-mercaptobenzoic acid (4-MBA) modified Au@Ag NPs to detect kanamycin. The detection range was 6.67×10^{-10}–2×10^{-7} g mL^{-1}, and the LOD was 142 pg mL^{-1}. It has excellent sensitivity and selectivity for real milk samples. Wang *et al.*[109] further optimized the detection system, and constructed a kanamycin SERS sensor through a nucleic acid aptamer controlled zinc-doped carbon quantum dot catalytic switch and a size-controllable Au nanorod. This detection range was 10^{-12}–10^{-5} g mL^{-1}, the LOD was 3.03×10^{-13} g mL^{-1}, showing higher detection sensitivity and better quantitative ability. This shows that in the design of SERS sensors, the performance of the sensor can be significantly improved by optimizing the composition and structure of nanomaterials. Chen *et al.*[110] developed a novel kanamycin SERS aptamer sensor by using DNA hydrogel network to capture plasma core–shell nanoparticles from another perspective. The LOD was 2.3 fM, which reflects the innovation in the combination of nanomaterials and biomolecules, shows the possibility of achieving higher sensitivity detection by designing complex biological

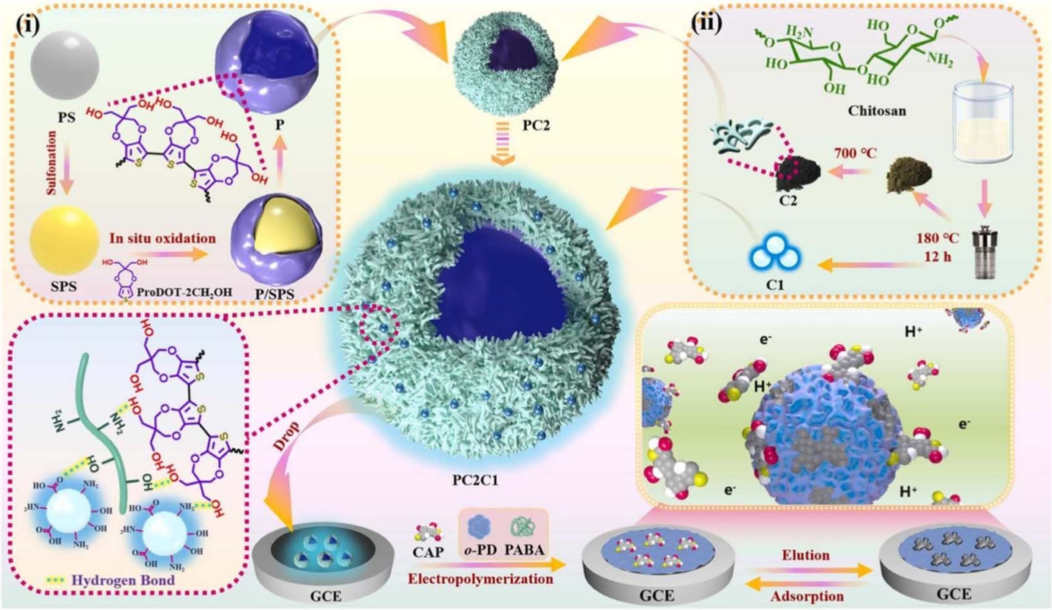

Fig. 9 Principle diagram of MIP sensor for high sensitivity analysis and determination of CAP, (this figure has been adapted/reproduced from ref. 104 from PUBLISHER *Journal of Hazardous Materials*, copyright 2024).

nanostructures. This comprehensive design idea from nanomaterials to biomolecular networks provides a new direction for the detection of antibiotics such as kanamycin, and also provides a richer strategy choice for subsequent research. Meng *et al.*[111] turned to the detection of another antibiotic, oxytetracycline (OTC), and studied a SERS sensor based on "hot spots" between Au NPs connected by DNA sequences. The innovation of the research is to use the specific binding of aptamers to target molecules to regulate the aggregation of nanoparticles, thereby enhancing the Raman signal. This method LOD was 4.35×10^3 fg mL^{-1}, demonstrated a high degree of selectivity (Fig. 10a). This shows that in the design of SERS sensors, efficient detection of different antibiotics can be achieved by skillfully using the specific recognition of biological molecules and the physical properties of nanoparticles. This also provides a reference for the design of other similar detection systems, it is an effective strategy to enhance the signal by regulating the aggregation of nanoparticles. Li *et al.*[112] further expanded this idea and studied a tetracycline (TTC) targeted response release SERS sensor based on aptamer gated HP-UiO-66-NH_2 nanochannels. The innovation of the research is to combine the aptamer with the nanochannel, and trigger the response of the nanochannel through the combination of the target molecule, thereby realizing the release and enhancement of the signal. This method detection range was 0.01–10^4 ng mL^{-1} and the LOD was 0.01 ng mL^{-1}, shows good practical application performance, such as high recovery in real samples. This indicates that in the design of SERS sensors, the combination of aptamers with new nanostructures such as nanochannels can achieve more complex and efficient detection mechanisms.

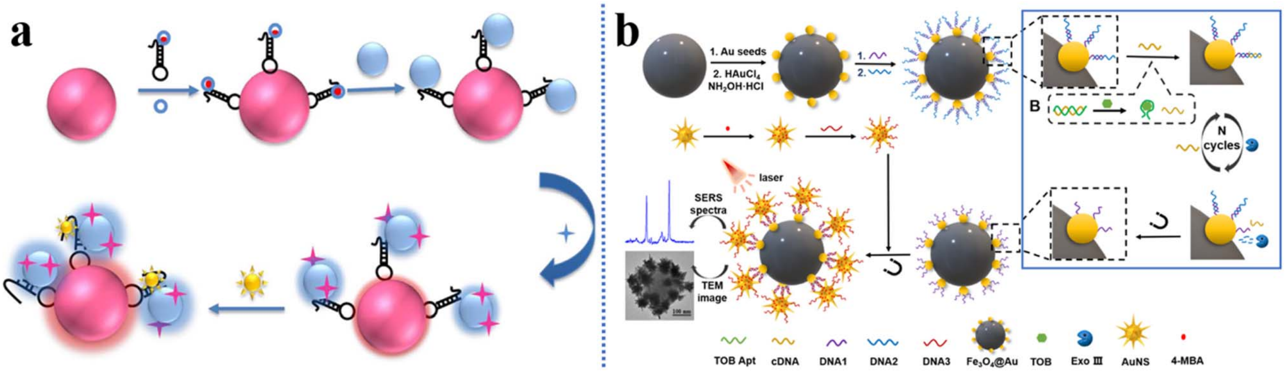

Fig. 10 (a) DNA sequence ligation Au NPs ultra-sensitive detection of OTC in aquatic products (this figure has been adapted/reproduced from ref. 111 from PUBLISHER *Talanta*, copyright 2017), (b) BMPSNs for ultrasensitive detection of TOB (this figure has been adapted/reproduced from ref. 113 from PUBLISHER *Biosensors and Bioelectronics*, copyright 2022).

This transition from nanoparticle aggregation to nanochannel response provides a richer design idea for antibiotic detection, and also provides a new direction for the detection of other biomolecules. Zhao *et al.*[113] prepared magnetic nanoparticles (Fe_3O_4)–Au NPs–AuNSs bilayer magnetoplasmonic satellite nanoassemblies (BMPSNs) for ultrasensitive detection of tobramycin (TOB). The innovation of this method is to use the combination of magnetic nanoparticles and plasma nanoparticles to construct a detection system with high sensitivity. This method achieves a very low detection limit was 0.44 fg mL^{-1}, shows good anti-interference ability. This indicates that in the design of SERS sensors, more efficient signal enhancement and more specific detection can be achieved by combining different types of nanomaterials (such as magnetic nanoparticles and plasma nanoparticles) (Fig. 10b). This also provides a reference for the design of other similar detection systems, to improve the performance of the sensor by constructing complex nanoassemblies. Fang *et al.*[114] further expanded the detection idea and studied an antibiotic detection method for CAP by synergistic enzyme-assisted SERS technology with aptamer conformation. Enzyme-assisted DNA amplification technology is used to enhance the signal. By designing specific nucleic acid oligonucleotide chains, highly selective recognition and efficient amplification of target molecules are achieved. This method LOD was 15 fM, shows a good practical application prospect. This indicates that in the design of SERS sensors, ultrasensitive detection of trace antibiotics can be achieved by combining specific recognition of biomolecules and enzyme-assisted amplification technology. This transformation from nanomaterial assembly to biomolecular amplification provides a richer strategy choice for antibiotic detection, and also provides new ideas for the detection of other biomolecules.

3.2.3 Antibody modification. Antibody is another kind of commonly used biological recognition element with high specificity and affinity. By immobilizing the antibody on the SERS substrate, the specific capture and detection of antibiotics can be achieved. Antibody-modified SERS sensor can effectively reduce non-specific adsorption and improve the accuracy and sensitivity of detection when detecting antibiotics.[115] A new sensor based on competitive SERS immunoassay and magnetic separation proposed by Yang *et al.*,[116] demonstrated high sensitivity and selectivity in the detection of residual CAP. This method achieves rapid detection in a wide concentration range by combining functionalized Au NPs and magnetic nanoparticles (MNP). This study provides a new idea for the application of SERS technology in antibiotic detection. Li *et al.*[117] further explored the application of SERS technology in the detection of two antibiotics in dairy products. They used lateral flow (LF) combined with SERS to achieve dual detection of two β-lactam antibiotics in milk powder. The SERS spectra were analyzed by peak height method and multiple linear regression (MLR), which proved the potential of this method in real-time multiple quantitative analysis of antibiotics (Fig. 11a). Pan *et al.*[118] further improved the sensitivity and stability of SERS technology in antibiotic detection. They developed a SERS-based LFA strip, using core–shell Au@Ag NPs as SERS tags to achieve ultrasensitive quantitative analysis of CAP, thiamphenicol (TAP) and florfenicol (FFC) (Fig. 11b). Compared with the previous two studies, this study significantly improved the stability and repeatability of detection by improving the design of SERS tags, and provided a more reliable solution for the application of SERS technology in antibiotic detection. With the continuous development of the application of SERS technology in the detection of antibiotics, from the initial high-sensitivity detection, to the multiple detection in complex matrices, to the ultra-sensitive and high-stability quantitative analysis, it shows its broad prospects in the field of analytical chemistry.

SERS technology combined with aptamer or antibody modification strategies has shown excellent performance in antibiotic detection, especially in the targeted capture of low-concentration antibiotics, achieving ultra-low detection limits and providing strong technical support for high-sensitivity detection of antibiotics.

3.2.4 Raman reporter coding. Reporter coding is an important functional modification strategy in SERS technology. By encoding molecules with unique Raman spectral characteristics into SERS probes, high sensitivity detection of antibiotics can be achieved.[119] As two commonly used reporter, 5,5-dithiobis-2-nitrobenzoic acid (DTNB) and 4-MBA have strong Raman signals and good stability. 4-MBA is a benzoic acid derivative containing sulfhydryl groups, which can form stable chemical bonds with the surface of metal nanoparticles through sulfhydryl groups, thereby achieving efficient SERS signal enhancement. The Raman characteristic peak of 4-MBA is obvious, which can be used as a reporter in SERS probe to detect target molecules such as antibiotics.[120] DTNB is an aromatic compound containing thiol groups, which has strong Raman signal and good stability. DTNB can form stable chemical bonds with the surface of metal nanoparticles through thiol groups, thereby achieving efficient SERS signal enhancement. The Raman characteristic peak of DTNB is obvious, which can be used as a reporter in SERS probe to detect target molecules such as antibiotics.[121] Fan *et al.*[122] established a side-stream immunosensor based on dual SERS for simultaneous detection of tetracycline and penicillin residues in milk. The newly synthesized Au@Ag NPs were labeled with different Raman molecules, including DTNB or 4-MBA, and then conjugated with anti-tetracycline monoclonal antibody or anti-penicillin receptor to form two SERS nanoprobes. These two nanoprobes can recognize tetracycline-BSA and ampicillin-BSA, respectively, which is conducive to the simultaneous detection of two types of antibiotics on a test line. After optimization, the LOD of tetracycline and penicillin were 0.015 ng mL^{-1} and 0.010 ng mL^{-1}, respectively. The recoveries were 88.8–111.3%, and the relative standard deviations of detection accuracy were less than 16%.

In the future, with the continuous development of nanomaterial science and SERS technology, functional modification strategies will be continuously improved to provide more efficient and sensitive solutions for antibiotic detection and other biomolecular detection.

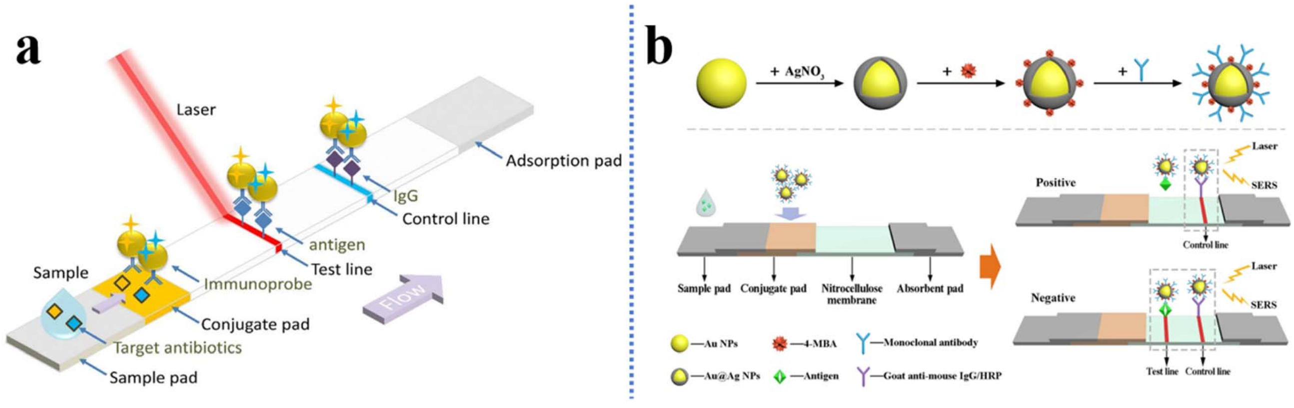

Fig. 11 (a) Dual detection of cefalexin and ampicillin in milk powder by LF combined with SERS (this figure has been adapted/reproduced from ref. 117 from PUBLISHER *Food Analytical Methods*, copyright 2017), (b) antibody-modified Au@Ag NPs for quantitative detection of target CAP, TAP and FFC in LFA bands (this figure has been adapted/reproduced from ref. 118 from PUBLISHER *Food Analytical Methods*, copyright 2021).

3.3 SERS substrate performance evaluation criteria

In the application of SERS technology in the field of antibiotic detection, the evaluation of substrate performance is very important, which directly determines the sensitivity, accuracy and reliability of the detection. The substrate performance mainly evaluates the enhancement factor, signal reproducibility and long-term stability.[123]

3.3.1 Enhancement factor (EF). EF is one of the key indicators to measure the performance of SERS substrates, which reflects the ability of the substrate to enhance the Raman signal. The calculation of EF usually involves the comparison of the SERS signal with the ordinary Raman signal intensity, and the expression is: $\mathrm{EF} = \frac{I_{\mathrm{SERS}}}{I_{\mathrm{Raman}}} \times \frac{N_{\mathrm{Raman}}}{N_{\mathrm{SERS}}}$, I_{SERS} and I_{Raman} are SERS and ordinary Raman signal intensity, respectively. N_{SERS} and N_{Raman} are the number of molecules in SERS and ordinary Raman detection, respectively. The higher the EF value, the better the enhancement effect of the substrate. In practical applications, distinguishing the contributions of EM and CM are crucial for understanding the enhancement mechanism of the substrate. The EM is mainly due to the local surface plasmon resonance effect on the substrate surface, while the CM is related to the chemical interaction between the molecule and the substrate. In general, a high-performance SERS substrate should have an $\mathrm{EF} \geq 10$, which means that the substrate can significantly enhance the Raman signal, thereby improving the sensitivity of the detection.[124]

In recent studies, Wang *et al.*[125] designed a novel Cloverleaf Hollow Fiber (CHF) for SERS detection of photofluids in optical fibers. The design significantly increases the contact area between the test liquid and the enhanced substrate by introducing four air holes inside the fiber, thereby simplifying the liquid injection process. In this study, Ag NPs were modified inside the fiber as a Raman enhancement substrate. Highly sensitive SERS detection is achieved by using the evanescent field of the fiber to excite the Raman signal. With R6G as the target analyte, the LOD was 10^{-11} M, the EF was 1.59×10^{8}, and the RSD was 4.8%, showing excellent sensitivity and repeatability. In addition, the fiber was also successfully used to detect enrofloxacin solution, which further verified its stability and reliability in antibiotic detection. This CHF-based SERS sensor not only has important application potential in food safety, environmental monitoring and other fields, but also provides a new technical means for trace analysis in biomedical and agricultural fields.

3.3.2 Signal reproducibility. Signal reproducibility is another important indicator to evaluate the performance of SERS substrates, which reflects the consistency of SERS signals generated by the substrates under different conditions. The signal reproducibility is usually measured by the RSD. The lower the RSD value, the better the signal reproducibility of the substrate. In practical applications, RSD < 10% is considered to meet the requirements, which means that the substrate can provide stable and reliable SERS signals under different detection conditions. The reproducibility of the signal directly affects the accuracy and reliability of the detection results. Therefore, in practical applications, it is necessary to strictly control the preparation process and detection conditions of the substrate to ensure the reproducibility of the signal.[126]

Huang *et al.*[127] developed a SERS detection substrate based on aluminum foil (AlF), combined with a multi-layer perceptron (MLP) deep learning model for rapid identification of antibiotic components in the mixture. The experimental results show that the detection method exhibits excellent performance, and the EF reached 4.2×10^{5}. The detection sensitivity of fleroxacin, levofloxacin, pefloxacin, sulfadiazine, methylene blue and malachite green is excellent. In addition, the preparation process of aluminum foil-based SERS substrate does not need to add organic reagents, and has good repeatability, RSD < 9.6%. Combined with the MLP model, this method can accurately identify the mixed pollutants of sulfadiazine, methylene blue and malachite green, and the recognition accuracy is 97.8%. The Shapley Additive Explanations (SHAP) analysis further shows that the MLP model can focus on the distribution of characteristic peaks, thereby achieving accurate identification of complex pollutants. It provides a potential method for the detection and identification of antibiotics and disinfectants in actual aquaculture wastewater, demonstrating the strong performance and good robustness of the MLP model in complex matrices.

3.3.3 Long-term stability. Long-term stability is an important indicator to measure the performance retention of SERS substrates during long-term use. In the practical application of antibiotic detection, the substrate needs to maintain its activity for a long time to ensure the accuracy and reliability of the detection results. Usually, the long-term stability is evaluated by the activity retention rate within 30 days, and the activity retention rate >80% is considered to be the standard for the good long-term stability of the substrate. This means that the substrate can maintain more than 80% of its initial activity within 30 days, thus ensuring that the performance of the substrate will not decrease significantly during long-term use. In order to improve the long-term stability of the substrate, it is necessary to conduct in-depth research on the selection of substrate materials and the optimization of preparation process.[128]

Zhang *et al.*[129] proposed a flexible SERS substrate based on Ag composite deep eutectic solvent (DES) gel, which was specially designed for low-temperature antibiotic detection. This study effectively solved the problem of low response of antibiotics in SERS detection by using R6G to label the target antibiotics. This novel SERS substrate has excellent mechanical strength, stability and frost resistance, can directly and sensitively detect four types of six antibiotics in frozen chicken wings at 25 °C with a LOD less than 1.3×10^{-9} M. In addition, the substrate exhibits excellent uniformity, RSD < 6.4%, reproducibility RSD < 6.2%, and long-term stability up to 30 days, ensuring high sensitivity and quantitative antibiotic detection. Theoretical analysis shows that the binding energy between the labeled antibiotics and the Ag surface is higher, which further improves the detection sensitivity. This innovative technology provides new possibilities for the quantitative detection of antibiotics in frozen foods and heralds a new era of extended detection of a wider range of antibiotics at low temperatures.

4. SERS strategy for antibiotic detection

4.1 Direct method

The direct detection method of SERS technology is a detection method that doesn't depend on the marker. Its core advantage is that it can directly detect the antibiotic molecules in the sample, which greatly simplifies the detection process and improves the detection efficiency.[130] This method significantly enhances the Raman scattering signal of antibiotic molecules by using SERS active substrates, such as metal nanoparticles or nanostructured surfaces, so that high sensitivity detection can be achieved even at extremely low concentrations. Researchers have developed a SERS substrate based on Au NPs, and successfully achieved direct detection of tetracycline in water with a LOD of nmol L^{-1}.[131] In addition, the direct detection method also has the advantages of simple operation and rapid response, which makes it have broad application prospects in the fields of environmental monitoring and food safety testing.

4.1.1 Construction of characteristic peak attribution database. In order to achieve accurate identification and quantitative analysis of antibiotics, it is one of the key steps to construct a characteristic peak attribution database. By combining density functional theory (DFT) calculations, the vibration modes and corresponding Raman characteristic peaks of antibiotic molecules can be simulated, thus providing theoretical support for the experimentally observed SERS spectra. Specifically, DFT calculation can accurately predict the geometric structure, vibration frequency and Raman activity of molecules. These information correspond to the characteristic peaks of SERS spectrum obtained in the experiment, so as to realize the accurate attribution of the characteristic peaks.[132] In the study of sulfonamide antibiotics, the frequency of the main vibration modes and the corresponding Raman activity were obtained by DFT calculation. These calculation results are highly consistent with the characteristic peaks in the experimental spectra, which provides a reliable basis for the identification of sulfonamide antibiotics.[133] The construction of the characteristic peak attribution database can also establish a systematic database by collecting a large number of SERS spectral data of different antibiotics and combining the DFT calculation results to provide a reference for subsequent antibiotic detection and analysis.

Chen *et al.*[134] designed and prepared a SERS substrate based on COFs loaded Ag NPs (COF@Ag) for highly sensitive detection of amoxicillin (AMX) in lake water and honey. Through a series of material characterization methods, the key mechanism of COFs in SERS detection was deeply explored. The frontier electronic orbital properties of COFs and AMX were analyzed by DFT simulation. Combined with the interaction region indicator (IRI) method, the chemical bonds and weak interactions in the system were systematically studied, which provided a theoretical basis for revealing the SERS enhancement mechanism. The results show that COFs can effectively enrich Ag NPs, thus forming a denser hot spot distribution on the substrate and significantly enhancing the electromagnetic field effect. In aqueous solution, the linear detection range of this method for AMX was 1–30 μg L^{-1}, and the LOD was 0.279 μg L^{-1}. Highly sensitive and selective detection of AMX in lake water and honey was achieved. Through DFT simulation and IRI analysis, the enhancement mechanism of COFs in SERS detection is deeply revealed, which provides important theoretical support and practical guidance for the further application of COFs in SERS field.

4.1.2 Spectral deconvolution algorithm for simultaneous multi-component detection. In practical applications, there are often a variety of antibiotics or other interfering substances in the sample, which makes the SERS spectrum complicated and the characteristic peaks overlap seriously, which brings challenges to quantitative analysis.[135,136] In order to solve this problem, the spectral deconvolution algorithm is introduced into SERS technology, and the overlapping spectral signals are separated by mathematical method, so as to realize the simultaneous detection of multiple components. The core idea of the spectral deconvolution algorithm is to decompose the complex spectral signal into a series of simple spectral components, each corresponding to a specific component in the sample. By establishing the relationship between spectral components and component concentrations, quantitative analysis of each component can be achieved.[137] In the detection of complex samples containing multiple antibiotics, the researchers used spectral deconvolution algorithms such as non-negative least squares (NNLS) and independent component analysis (ICA) to successfully separate overlapping spectral signals and accurately quantify the concentration of each antibiotic.[138] The spectral deconvolution algorithm can also be combined with other chemometric methods, such as principal component analysis (PCA) and partial least squares discriminant analysis (PLS-DA), to further improve the accuracy and reliability of multi-component detection.[139]

Mou *et al.*[140] constructed a human milk system containing doxycycline (DXC) or tetracycline (TC) residues, and applied machine learning models and clustering algorithms to classify and predict the insufficient concentration of antibiotics in a single system and a mixed system. This goal is achieved by unlabeled SERS spectra. The experimental results show that the convolutional neural network (CNN) model has a recognition accuracy of 98.85% under the optimal hyper-parameter combination. In addition, independent component analysis (ICA) and pseudo-Siamese convolutional neural network (pSCNN) were used to quantitatively analyze the proportion of antibiotics in mixed human milk samples. Combining SERS technology with machine learning algorithms shows great potential for rapid identification and accurate quantification of under-concentration antibiotics in single and mixed systems in human milk. This study provides a new technical means for the detection of antibiotic residues, and provides a scientific basis for ensuring infant health.

4.2 Indirect method

The promising detection strategy of SERS technology is indirect detection method, which skillfully uses competitive aptamer sensors to achieve high sensitivity detection of antibiotics. The researchers designed an aptamer sensor based on Au NPs, which is modified with a specific aptamer on the surface and can specifically bind to the target antibiotic molecule. During the detection process, the antibiotics to be tested and the reference substance labeled with Raman signal molecules competitively bind to the aptamer. When the concentration of antibiotics in the sample is high, more molecules to be tested bind to the aptamer, resulting in the replacement of the marker, which in turn leads to a significant change in the SERS signal. Quantitative analysis of antibiotic concentration can be achieved by accurately measuring this signal change.[141] This competitive aptamer sensor has high selectivity and sensitivity, has simple operation and fast response, which provides the possibility for rapid detection and real-time monitoring. Wang *et al.*[142] used 6-carboxy-X-rhodamine (ROX) -labeled aptamers and 4-mercaptobenzonitrile (4-MBN) functionalized Au NPs as SERS probes to construct a reliable and rapid method for the detection of enrofloxacin. Under the optimal conditions, the developed SERS aptamer sensor had a correlation coefficient R^2 was 0.98 and a detection range was 5 nM–1 μM, the LOD was 0.12 nM, and a recovery rate of 93.6–112.0%. The established SERS aptamer sensor is sensitive, reliable and fast, and is expected to be applied to the on-site detection of enrofloxacin in complex substrates.

In addition, the enzyme-catalyzed signal amplification system also provides strong support for the application of SERS technology in antibiotic detection. Among them, the regulation of peroxidase mimic activity is an important signal amplification strategy. Some nanomaterials, such as Fe_3O_4 NPs, can simulate the activity of peroxidase, catalyze the decomposition of hydrogen peroxide to produce hydroxyl radicals, and then trigger color reaction or enhance SERS signal.[141] In antibiotic detection, these nanozymes can be combined with aptamer sensors. In the presence of target antibiotics, a series of cascade reactions are triggered to activate the catalytic activity of nanozymes, resulting in a significantly amplified SERS signal.[143] This signal amplification effect greatly improves the sensitivity of the detection, so that the presence of antibiotics can be accurately detected even at extremely low concentrations.

4.3 Dual-mode and multi-mode detection technologies

Although SERS technology exhibits exceptional sensitivity, its single-mode detection faces practical challenges: On one hand, SERS signals are susceptible to interference from substrate uniformity, laser fluctuations, and sample matrices, compromising quantitative reliability;[144] on the other hand, Raman signals alone struggle to distinguish non-specific adsorption from genuine signals, posing a false-positive risk. To overcome these limitations, researchers have integrated SERS with one or more alternative detection modes (*e.g.*, colorimetry, fluorescence, or electrochemistry) onto a single sensing platform, establishing dual-mode or multimodal collaborative detection strategies.[145] These modes complement each other: one mode enables rapid screening or visual qualitative analysis, while the other delivers high-sensitivity quantitative measurements. Their mutual validation significantly enhances detection accuracy and interference resistance.

In dual-mode detection, SERS-colorimetric dual-mode sensors have been extensively investigated. The colorimetric method offers the advantages of visualization and the absence of complex instrumentation, albeit with typically low sensitivity; conversely, SERS exhibits superior sensitivity. Their combination enables a hierarchical detection approach combining "visual preliminary screening + Raman-based precise quantification". Li *et al.*[146] constructed a ratio-based SERS-colorimetric dual-mode sensor for tetracycline by leveraging the localized surface plasmon resonance (LSPR) properties of Au NPs and a 4-MBA-labeled SERS probe. Tetracycline interacts with the enol groups in its molecular structure to induce nanoparticle aggregation, resulting in a color transition from red to blue-purple and a red shift in the UV-visible absorption spectrum. The SERS signal intensity exhibits a good linear relationship with tetracycline concentrations within the range of 0.1–10 μmol L^{-1}, with a detection limit of 0.058 μmol L^{-1}.[147] This method demonstrated excellent recovery rates and interference resistance in both actual water and milk samples.

The SERS-fluorescence dual-mode sensor has also garnered significant attention. The fluorescence mode exhibits high sensitivity and rapid response but is susceptible to photobleaching and background fluorescence interference; in contrast, the SERS mode provides fingerprint spectral information. The combined use of these two modes enables orthogonal validation of the target analyte. Qi *et al.*[148] developed an Ag@NH_2-MIL-101 nanoprobe for SERS-fluorescence dual-mode detection of tetracycline antibiotics. In the fluorescence mode, photoinduced electron transfer between the antibiotic molecules and the MOF framework induces fluorescence quenching; in the SERS mode, Ag NPs generate electromagnetic field enhancement. The dual-mode signal changes exhibit a linear relationship with tetracycline concentrations across five orders of magnitude, with a detection limit of 7.6×10^{-5} ppm and satisfactory recovery rates in actual water samples and milk samples. This dual-mode strategy effectively avoids false-positive or false-negative results associated with single-mode detection.

In multimodal detection, the SERS-fluorescence-electrochemical tri-modal sensor represents a cutting-edge integrated strategy. This tri-modal detection method cross-verifies the same target through three independent signal transduction mechanisms, theoretically eliminating misjudgments caused by matrix interference and operational errors. Researchers integrate the SERS-active substrate (*e.g.*, Au@Ag NPs), fluorescent probes (*e.g.*, quantum dots), and electrochemical working electrodes onto a single microelectrode or microfluidic chip.[149,150] In the presence of the target antibiotic, the three signals exhibit synchronous or synergistic changes. Although the fabrication process and signal decoupling of the tri-modal sensor are relatively complex, its ultra-high accuracy in trace concentrations and complex matrices (*e.g.*, whole blood, tissue homogenates) positions it as a key development direction for advanced detection platforms.[151] Current research primarily focuses on the proof-of-concept stage; future integration with microfluidic technologies and automated analytical instruments will facilitate its practical application.

4.4 Microfluidic integrated system

The microfluidic integrated system combined with microchamber concentration enrichment technology provides a more efficient and accurate sample processing platform for SERS detection. By designing a specific microchamber structure in the microfluidic chip, efficient enrichment and concentration of antibiotics can be achieved, thereby significantly improving the detection sensitivity. The integration of SERS technology and microfluidic chip provides a new solution for the automation and high-throughput detection of antibiotics.[152,153] Microfluidic chip technology has been widely used in the field of biomedical detection due to its advantages of precise control of fluid flow, low sample consumption and fast analysis speed. By integrating SERS substrates into microfluidic chips, automatic sample injection, reaction, detection and data analysis can be realized, which greatly improves the detection efficiency and accuracy.[154] This integrated design simplifies the experimental operation process, reduces the human error, which makes it possible for on-site rapid detection and instant diagnosis.

Nguyen *et al.*[97] successfully constructed a low-blinking SERS substrate for the detection of kanamycin by developing a nanocomposite based on graphene oxide (GO) and Au NPs. The sensor can be reused with a LOD was 0.75 nM and a detection range was 1–100 nM (Fig. 12). The detection system can be potentially used for sensitive and reliable analysis of small molecules, which solves the common flicker problem of traditional SERS substrates in microfluidic detection systems. This innovative substrate design provides a new idea for the application of SERS technology in complex samples. The research of Patze *et al.*[155] further expanded the application potential of SERS technology in environmental science. Using SERS and microfluidic cartridge systems, they have achieved quantitative detection of sulfamethoxazole in the nanomolar range. This study verified the high efficiency of SERS technology in the detection of low concentration targets, demonstrated the practical application value of this method in environmental monitoring by using surface water samples as substrates. This is in good agreement with the research of Nguyen *et al.* The former improves the stability and sensitivity of SERS detection through material innovation, while the latter applies this technical advantage to the field of environmental science, which further proves the wide applicability and powerful detection ability of SERS technology in different application scenarios.

Table 1 summarizes and compares the literature methods of SERS technology for antibiotic detection, as follows:

Microfluidic integrated systems demonstrate unique advantages in antibiotic SERS detection: their micron-scale channels can precisely manipulate micro-volume samples (from μL to nL), achieving automatic sampling, mixing, and enrichment, significantly reducing reagent consumption and improving detection throughput and reproducibility; the enclosed microenvironment can reduce external contamination and oxidation of silver substrates, extending substrate stability; multi-module integration (filtration, extraction, labeling, detection) enables the chip to perform full analysis from "sample in to result out".[152,170] Future development should focus on high-throughput multi-channel arrays to simultaneously detect multiple antibiotics, integrating miniature valves and pumps to achieve fully automated portable devices, functionalizing the channel surfaces (such as with molecular imprinting

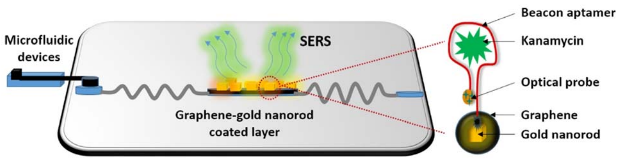

Fig. 12 GO and Au NPs composite materials for microfluidic detection system (this figure has been adapted/reproduced from ref. 97 from PUBLISHER *Sensors and Actuators B: Chemical*, copyright 2019).

Table 1 The detection performance of sensors based on different SERS substrates for antibiotics was studied

Detecting object	Substrate material	Performance evaluation	Range of linearity	LOD	Reference
Ampicillin trihydrate, tetracycline hydrochloride	Ag NPs/CNT-GO membranes	Long-term stability 70 days	4.0×10^{-9}–1.0×10^{-6} M, 2.0×10^{-9}–6.0×10^{-7} M	3.2×10^{-9} M, 1.5×10^{-9} M	96
14 Kinds of antibiotics	Ag nanofilm	Signal reproducibility	—	10^{-5} M	156
Ciprofloxacin, norfloxacin, enrofloxacin, amoxicillin, cefazolin, doxycycline hydrochloride	Ag octahedra	EF = 3.62×10^{7}, signal reproducibility RSD = 5.36%	10^{-4}–10^{-9} M, 10^{-4}–10^{-9} M, 10^{-4}–10^{-10} M, 10^{-4}–10^{-10} M, 10^{-4}–10^{-9} M, 10^{-4}–10^{-10} M	0.60 nM, 0.21 nM, 0.058 nM, 0.063 nM, 0.72 nM, 0.057 nM	157
Enrofloxacin hydrochloride	Ag NPs membranes	Signal reproducibility	1.0–200 nM	0.01 nM	158
Ciprofloxacin	Ag NSs	EF = 4×10^{9}	3×10^{-8}–3×10^{-5} M	6.9×10^{-10} M	159
Carbenicillin disodium	Ag NPs	—	1.0×10^{-8}–1.0×10^{-3} M	0.63×10^{-8} M	160
Ciprofloxacin, levofloxacin	GNRS@Ag	Signal reproducibility, RSD = 1.47%, RSD = 4.01%	10^{-6}–10^{-10} M	10^{-10} M	161
Ciprofloxacin, levo-floxacin, norfloxacin	Fe_3O_4@COF@Ag	EF = 2.32×10^{7}	1×10^{-8}–1×10^{-4} M, $1 \times 10^{-7.5}$–1×10^{-4} M, $1 \times 10^{-7.5}$–1×10^{-4} M	5.61×10^{-9} M, 1.44×10^{-8} M, 1.56×10^{-8} M	162
Tetracycline hydrochloride, oxytetracycline hydrochloride, doxycycline hydrochloride	Ag@NH_2-MIL-101(Al)	Signal reproducibility, RSD = 2.52%	9.62×10^{-5}–9.62 ppm, 9.94×10^{-5}–9.94 ppm, 1.03×10^{-4}–10.25 ppm	9.62×10^{-5} ppm, 9.94×10^{-5} ppm, 1.03×10^{-4} ppm	163
Ampicillin	Au NPL array/MgF_2/Au mirror/glass substrate	Signal reproducibility, RSD = 3.12%	10 fM–1 nM	3.1 fM	164
Ciprofloxacin, tetracycline, chloramphenicol	V_5S_4 NPPs	EF = 1.9×10^{8}	10^{-4}–10^{-7} M	10^{-7} M, 10^{-7} M, 10^{-8} M	165
Amoxicillin, tetracycline hydrochloride, ofloxacin	AgNPs/GNRs arrays	EF = 1.26×10^{5}	5×10^{-5}–200 μM, 1.5×10^{-5}–100 μM, 3×10^{-5}–50 μM	1.8×10^{-5} μM, 0.5×10^{-5} μM, 1.5×10^{-5} μM	166
Enrofloxacin, enoxacin, chloramphenicol	TiO_2 nanoparticle/ZnO quantum dot	EF = 4.8×10^{7}	10^{-3}–10^{-9} M	9.62×10^{-10} M 8.57×10^{-10} M 8.60×10^{-10} M	167
Penicillin potassium, tetracycline hydrochloride, levofloxacin	Au@4-MBN@SiO_2	Long-term stability, 24 weeks	10^{-3}–10^{-7} M, 10^{-3}–10^{-7} M, 10^{-4}–10^{-8} M	26.9 nM, 28.2 nM, 2.4 nM	168
Oxytetracycline	NH_2-UiO-66(Zr)@Au NPs	—	1.0×10^{-13}–1.0×10^{-6} g L^{-1}	10^{-10} g L^{-1}	169

or aptamer brushes) to enhance selectivity, combining machine learning algorithms to deconvolute overlapping signals in real time and correct matrix effects, and using low-cost degradable materials (such as paper-based or thermoplastic chips) to design disposable or renewable chips, thereby reducing the cost per test and promoting the large-scale application of SERS-microfluidic technology in rapid on-site multi-residue monitoring in food and environmental samples.

4.5 Machine learning-assisted SERS analysis

For the issues of high dimensionality, overlap, and noise interference in SERS spectral data, machine learning algorithms provide powerful analytical tools for antibiotic detection. In terms of classification and recognition, multilayer perceptrons (MLP) and convolutional neural networks (CNN) can automatically extract hierarchical spectral features, achieving high accuracy in the identification of mixed antibiotics—for example, MLP achieves a recognition accuracy of 97.8% for various aquatic pollutants,[119] and CNN achieves a classification accuracy of 98.85% for antibiotics in human milk.[171] In terms of quantitative prediction, methods such as independent component analysis (ICA) combined with pseudo-twin CNN (pSCNN) can establish nonlinear regression models between spectral signals and antibiotic concentrations, enabling simultaneous quantitative detection of multiple antibiotics in complex matrices,[97,132,155] with detection limits reaching nM to pM levels, significantly outperforming traditional linear calibration methods.

In terms of feature extraction, autoencoders and ICA can separate the independent characteristic spectra of each component from overlapping SERS spectra, effectively removing noise and redundant information, retaining the feature subsets most relevant to the type and concentration of antibiotics, and can also be used to assess the uniformity of the substrate surface and the distribution of "hot spots".[130] Overall, the deep integration of machine learning and SERS is driving antibiotic detection towards high throughput, high accuracy, and intelligence; in the future, with the embedding of interpretable deep learning models and edge computing chips into portable Raman instruments, it is expected to achieve fully automated on-site rapid detection from spectral acquisition to result output.

5. Challenges and breakthroughs of SERS technology in antibiotic detection

5.1 The balance between sensitivity and reproducibility

SERS technology has shown great potential in the field of antibiotic detection due to its excellent sensitivity, which can realize the detection of extremely low concentration antibiotic molecules. However, in practical applications, the technology faces the challenge of balancing sensitivity and reproducibility. The generation of SERS signals depends on the nanostructure and surface properties of the substrate. The small difference in the preparation process, the inhomogeneity of the substrate quality, and the fluctuation of the detection environment will all lead to a significant decrease in signal reproducibility, thus hindering the further development of SERS technology.[172,173] In actual detection, different batches of SERS substrates may have different enhancement effects due to the instability of reaction conditions (such as temperature, reaction time, precursor concentration, *etc.*) in chemical synthesis. Even if the same substrate is tested at different times or in different laboratory environments, the signal intensity may fluctuate due to changes in environmental humidity, temperature and other factors. This reproducibility problem makes it difficult for SERS technology to obtain consistent and reliable detection results in practical applications.[174,175]

In order to solve this problem, it is particularly critical to develop a stable and controllable preparation process and standardized detection process. Optimizing the preparation process is one of the effective ways to improve the uniformity of the substrate. By improving the control of the reaction conditions of the chemical synthesis method, such as the use of accurate temperature control systems and strict time control procedures, it can be ensured that the substrates synthesized each time have highly consistent nanostructures and surface properties. In addition, combining the advantages of physical deposition method and chemical synthesis method, such as forming a uniform metal film on the surface of the substrate by physical vapor deposition method, and then growing nanostructures on the surface by chemical synthesis method, the uniformity and stability of the substrate can be further improved.[176] At the same time, it is also very important to develop a unified and standardized detection process. This includes standardized sample pretreatment methods, measurement conditions, *etc.* The influence of human factors on the test results can be effectively reduced by specifying the concentration range of the sample, the selection of the solvent, the laser power and the exposure time during the measurement. Through these measures, the reproducibility of SERS technology can be significantly improved while ensuring its high sensitivity, thus promoting its wide application in antibiotic detection.[175]

5.2 Complex matrix interference and quantitative calibration controversy

In the actual detection of antibiotics, food samples usually contain complex matrix components, such as pigments, proteins, fats, *etc.* These components will cause serious background signal interference to SERS detection, cover up or confuse the characteristic Raman signal of antibiotic molecules, thus seriously affecting the accuracy of detection.[177,178] When detecting antibiotic residues in milk, the protein and fat components in milk will produce a strong background signal, which makes the Raman signal of antibiotic molecules difficult to be accurately identified. For the problem of complex matrix interference, the development of multi-stage filtration technology is the key. In the sample pretreatment stage, most of the impurities can be removed by centrifugation, filtration and other methods. The solid particles and macromolecular proteins in the sample were removed by high-speed centrifugal separation, and then the residual suspended solids were removed by microporous membrane filtration.[179] In the detection process, it is also very important to design specific recognition elements to achieve selective enrichment. The specific recognition element prepared by molecular imprinting technology can specifically recognize and enrich antibiotic molecules like "lock and key", thus effectively reducing background interference.[180] Combined with microfluidic technology, a multi-stage separation structure is set up in the chip, which can further remove impurities before the sample enters the detection area and improve the selectivity and accuracy of the detection.[153,181] For quantitative calibration disputes, it is urgent to explore new calibration strategies. Combined with artificial intelligence technology, a large number of calibration data are analyzed and processed through machine learning algorithms to establish a more accurate quantitative model. This method can automatically identify and correct matrix effects and improve the reliability of quantitative results. The development of new markers to replace traditional isotope markers can reduce costs, eliminate biosafety risks. The use of fluorescent markers or magnetic markers to achieve quantitative calibration through their unique physical properties provides a new idea for the quantitative analysis of SERS technology in antibiotic detection.[182,183]

5.3 Advances in substrate design and surface functionalization strategies for addressing key challenges

During the transition of SERS technology from high-sensitivity laboratory detection to practical on-site antibiotic monitoring, three interrelated core challenges have consistently constrained its widespread application: First, macromolecular substances such as proteins, lipids, and humic compounds, which are abundant in complex samples, non-specifically adsorb onto the SERS substrate surface, blocking "hotspots" and generating strong background Raman signals that severely interfere with the identification of antibiotic characteristic peaks. Second, the Raman fingerprint spectra of structurally similar antibiotics exhibit high overlap, making it difficult for conventional SERS to achieve specific differentiation. Third, the non-uniform distribution of hotspots and variations in sample matrices result in poor quantitative reproducibility of SERS signals, failing to meet regulatory requirements for reliable quantification. Research over the past five years has demonstrated that rational substrate structure design and surface functionalization modifications represent the most effective approaches to overcoming these limitations.

To address the issue of complex matrix interference, researchers have developed a series of anti-contamination surface coatings and multilayered substrate structures that physically or chemically exclude large molecular interferents. Amphotericionic polymers grafted onto gold or silver nanostructure surfaces form a robust hydration layer that effectively resists protein adhesion while allowing small-molecule antibiotics to diffuse onto the metal surface. For example, Li *et al.*[117] found that polyethylene glycol-modified silver nanoparticles could reduce casein adsorption in milk by over 90%, enabling direct enrofloxacin detection without complex pretreatment. Another effective strategy involves coating the SERS active core (*e.g.*, Au@Ag) with a thin, mesoporous silica or MOF layer (with pore sizes of 2–10 nm), which acts as a molecular sieve: large molecular interferents such as proteins (>5 nm) and humic aggregates are effectively blocked, while antibiotic molecules (typically 0.8–1.5 nm) can freely diffuse into the internal hotspots. In the Fe_3O_4@COF@Ag substrate reported by Han *et al.*[175] the covalent organic framework layer not only enriched quinolone antibiotics but also effectively excluded humic acids from river water, improving the signal-to-noise ratio by nearly two orders of magnitude. The strategy combining the magnetic core with the SERS shell allows physical separation of captured antibiotics from matrix components *via* magnetic separation prior to SERS detection.[155] Following magnetic enrichment and washing, most proteins and lipids are removed, significantly suppressing matrix-induced signal suppression effects. The aforementioned anti-contamination and molecular sieve strategies demonstrate excellent performance in practical applications: when applied to spiked chicken meat and wastewater samples, the optimized substrates achieve recovery rates of 85–115% with an RSD below 10%, delivering detection performance comparable to traditional LC-MS/MS while significantly simplifying the sample processing workflow.

For the challenge of distinguishing structurally similar antibiotics, molecularly imprinted polymers (MIPs) and aptamer modification strategies provide essential molecular recognition capabilities. MIP films prepared using specific antibiotics as templates can form recognition cavities that are complementary to the target molecules in terms of size, shape, and functional group arrangement, enabling selective capture even in the presence of 10–100-fold excess structural analogs.[81] The silver nanoparticle membrane-based MIP sensor developed by Neng *et al.*[81] Exhibited excellent selectivity for enrofloxacin, with a cross-reactivity rate for ciprofloxacin below 5%. Dual-template MIP designs allow simultaneous capture of two antibiotics while excluding other analogs. Aptamers offer enhanced specificity through their precise three-dimensional folding structures; when anchored to Au@Ag nanostructures *via* thiol bonds, the resulting SERS aptamer sensor could distinguish oxytetracycline and tetracycline with a selectivity factor exceeding 20.[140] The key lies in the design of competitive or displacement detection modes: binding of the target antibiotic induces conformational changes in the aptamer, bringing the Raman reporter molecule closer to the "hot spot" or displacing it, thereby generating a significantly more discriminative target-specific signal change compared to bare SERS. Density functional theory calculations can predict the optimal binding orientation and binding energy between antibiotics and recognition elements, providing theoretical guidance for the rational design of functionally optimized monomers or aptamer sequences.[112] This approach has been successfully applied to distinguish sulfonamide drugs differing only in their heterocyclic substituents. Through these functional strategies, SERS sensors now routinely achieve a selectivity coefficient of 5–15 for target antibiotics compared to their closest structural analogs, which is sufficient to meet the requirements of most regulatory monitoring scenarios.

To address the long-standing challenge of insufficient quantitative reliability, surface functionalization offers multiple effective solutions, including the self-referencing internal standard method, ratio-based probes, and microfluidic integration. By immobilizing a Raman-inert reporter molecule alongside recognition elements on the same nanoparticle, an internal standard signal can be obtained to correct measurement fluctuations. The inter-batch and intra-point coefficient of variation for the ratio of antibiotic characteristic peak intensity to internal standard peak intensity is significantly lower than that for absolute intensity (where RSD typically exceeds 20%), with values ranging from 3–8%.[168] Chen *et al.*[169] employed the Au@4-MBN@SiO$_2$ substrate to simultaneously detect penicillin, tetracycline, and levofloxacin in water samples, achieving excellent linearity across four to five orders of magnitude (R^2 > 0.98). Ratio-based SERS aptamer sensors utilize aptamer probes designed with two distinct Raman reporter molecules—one permanently attached to the nanoparticle as a reference and the other released or drawn closer upon target binding-enabling intrinsic correction of substrate heterogeneity and matrix absorption effects through the ratio signal. Wang *et al.*[158] achieved reliable quantification of enrofloxacin in fish muscle tissue using a 4-MBN reference and ROX-labeled aptamer, with recovery rates ranging from 93.6% to 112.0%.[168] Integration of functionalized SERS substrates into microfluidic chips enables precise control over sample volume, flow rate, and mixing conditions. More importantly, automated online standard addition or calibration using on-chip internal standards significantly enhances quantitative accuracy in complex matrices.[127] The recently developed centrifugal microfluidic platform for meropenem detection in ICU plasma samples achieved outstanding performance with a daytime RSD below 8% through its built-in calibration channel.

5.4 Lack of long-term stability and exploration of new reinforcing materials

The long-term stability of SERS technology is another important issue in its practical application. Many SERS substrates will experience signal attenuation during long-term storage or use. The Ag substrate is easily oxidized due to its active chemical properties, resulting in the destruction of its surface nanostructures, thereby significantly reducing the detection sensitivity and reusability. This problem of insufficient long-term stability severely limits the application and promotion of SERS technology in practical detection.[184] In order to solve this problem, exploring new reinforcing materials has become a research hotspot. Metamaterials enhance the electromagnetic field distribution by designing sub-wavelength structures, which can achieve stable signal enhancement over a wide wavelength range. The single atom catalyst achieves specific recognition of specific molecules by enhancing the chemical enhancement effect, thereby improving the sensitivity and stability of the detection.[153] The development of degradable substrates and photothermal regeneration technology is also an important way to achieve green and sustainable detection. The cellulose nanocrystalline substrate has good biocompatibility and degradability, can be recycled by near-infrared laser treatment. This technology reduces the detection cost, reduces the impact on the environment, providing strong support for the sustainable development of SERS technology.[185,186]

In summary, although SERS technology faces many challenges in antibiotic detection, it is expected to achieve a balance between sensitivity and reproducibility, solve complex matrix interference and quantitative calibration disputes, and improve long-term stability by optimizing the preparation process, developing multi-stage filtration technology, and exploring new reinforcing materials. These breakthroughs will lay a solid foundation for the wide application of SERS technology in antibiotic detection and promote its further development in the fields of food safety and environmental protection.

Key challenge	Substrate/functionalization strategy	Representative antibiotic/matrix	Effect	Reference
Matrix interference (proteins, lipids, humus)	PEG/BSA-passivated Au@Ag NPs	Penicillin/milk	Non-specific adsorption decreased by 80%, with sensitivity maintained	117
	Fe$_3$O$_4$@MIPs magnetic separation	Clazoxillin/pig serum	Recycling rate > 80%, simplified pretreatment	106
	Microfluidic-C18 solid phase extraction	Sulfamethoxazole/surface water	The interference of humic acid decreases, with the detection limit reaching the nanomolar level	155
Structurally similar antibiotics for recognition	Ag@MIPs printed film	Enrofloxacin/ciprofloxacin	Selectively increase by 5 times	81
	Aptamer-gated HP-UiO-66-NH$_2$	Tetracycline/homologs	Only tetracycline response was observed, completely excluding interference	112
	pSCNN machine learning	Doxycycline + tetracycline/breast milk	The quantitative accuracy of the mixed ratio exceeds 98%	140
Quantitative reliability	Au@4-MBN@SiO$_2$ interior label	Penicillin, tetracycline/water quality	The intra-lot RSD is <6%, with a recovery rate of 90–110%	168
	Self-assembled hollow Ag octahedral arrays	8 Types of antibiotics/buffer solutions	RSD < 8%, good uniformity	157
	AI foil + MLP model	Sulfadiazine and other substances/aquaculture wastewater	Hybrid recognition accuracy is 97.8%	127

5.5 Commercial prospects of SERS antibiotic sensors

Commercialized SERS-based antibiotic sensors are transitioning from laboratory research to practical applications. Although currently commercially available mature products remain limited, several portable Raman spectrometers (such as those from brands like HORIBA, Ocean Insight, and B&W Tek) have been integrated with commercial or prototype SERS substrates (typically gold/silver nanostructures supported on glass, paper-based, or polymer films) for on-site screening of antibiotic residues in food, water, and clinical samples.[81] The primary commercial advantages of such sensors include: ultrahigh sensitivity, rapid response, molecular fingerprint specificity, simplified sample pretreatment (*e.g.*, through molecular sieve coating or anti-contamination surface modifications such as PEG or MIPs), and portability, making them highly attractive for regulatory monitoring and point-of-care testing applications.[82,129,176] However, its widespread application still faces several critical bottlenecks: poor batch-to-batch reproducibility of SERS substrates, insufficient long-term stability (particularly for oxidatively sensitive silver-based substrates), matrix interference in complex real-world samples, relatively high production costs, and the absence of universally recognized standardized operating procedures or regulatory certifications.[123]

In recent years, surface-enhanced Raman spectroscopy (SERS) antibiotic sensors have been rapidly transitioning from laboratory research to practical applications. Although commercially available mature products remain limited, multiple research teams have developed prototype technologies with commercial potential and achieved significant progress. For example, the team led by Tuan Vo-Dinh at Duke University developed a 3D plasma nanoflower SERS substrate based on gold nanostars, which, when fixed on hydrophobic tape,[187] enables direct detection of ciprofloxacin and ampicillin residues on chicken wings with detection limits of 3.3 nM and 1.5 nM, respectively. The substrate maintains stability for over six months with a relative standard deviation below 5%, demonstrating excellent potential for field applications. The nucleic acid aptamer-based tri-mode sensor and paper-tip SERS sensor developed by Cheng Yongqiang's team at Shandong University achieve a signal enhancement factor of 1.15×10^5 and a detection limit as low as 0.036 nM.[188] The multimodal design effectively prevents false-positive results, while the low-cost paper-tip substrate enables single-use operation and eliminates cross-contamination. Future commercialization efforts should focus on: utilizing scalable nanomanufacturing technologie to develop low-cost, highly uniform substrates; integrating internal standardization methods or ratio-based strategies for reliable quantification; introducing protective encapsulation or regenerative substrate designs to extend service life; and embedding machine learning algorithms into portable devices for automated spectral analysis.[177,178] The successful commercialization of SERS antibiotic sensors will not only bridge the gap between laboratory research and field applications, but also provide transformative tools for food safety assurance, environmental monitoring, and personalized antimicrobial therapy, ultimately contributing to the global fight against antibiotic resistance.

6. Conclusion

This review systematically summarizes the research advancements of SERS technology in detecting antibiotic residues in food and environmental matrices. The article provides an in-depth explanation of the synergistic mechanisms between electromagnetic enhancement and chemical enhancement, elucidates the spatial distribution characteristics of localized surface plasmon resonance "hotspots" and the regulatory effects of antibiotic molecular orientation on SERS signal intensity, and employs density functional theory calculations to clarify the intrinsic relationship between interfacial charge transfer processes and changes in molecular polarizability. These findings establish a robust theoretical framework and molecular-level mechanistic explanations for the rational design of high-performance SERS substrates. The review comprehensively evaluates material design strategies ranging from noble metal nanostructures and semiconductor–metal composites to flexible substrates and hybrid carbon/two-dimensional material platforms, as well as functionalization approaches such as molecularly imprinted polymers, nucleic acid aptamers, and antibody modification for enhancing detection selectivity. It constructs a holistic technical framework encompassing "substrate fabrication—surface functionalization—signal amplification", offering diverse technical pathways and solutions for developing highly sensitive and specific SERS sensing methods for complex real-world samples. At the application transformation level, this review addresses key bottlenecks hindering the field application of SERS technology—such as matrix interference, structural analog differentiation, and quantitative reliability—by examining cutting-edge strategies including microfluidic chip integration, multimodal collaborative detection, and machine learning-assisted spectral interpretation. It clarifies the development directions for standardizing, portability, and intelligence enhancement of SERS antibiotic sensors, providing crucial strategic guidance for transitioning this technology from laboratory research to practical applications such as rapid on-site food safety testing, real-time environmental water monitoring, and clinical antimicrobial resistance screening. These advancements offer transformative analytical for global antibiotic resistance governance and public health security.

Author contributions

Li Wang: conceptualization, formal analysis, investigation, data curation, writing – original draft. Fang Mi: writing – review & editing, supervision, project administration, funding acquisition. Hai Xue: writing – review & editing, funding acquisition. Xiaojiao Sun: formal analysis, data curation. Peng Chen: formal analysis, data curation, writing – original draft.

Conflicts of interest

There are no conflicts to declare.

Data availability

This review article does not involve the generation or analysis of new data. All data referenced and discussed in this review are available from the original published studies, which are cited in the text. Therefore, a data availability statement is not applicable.

Acknowledgements

This work is supported by the Natural Science Foundation of Xinjiang Uygur Autonomous Region (Youth Fund, 2024D01B62), Key Research and Development Task of Xinjiang Uygur Autonomous Region (2024B02014-2).

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