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Efficient Detection of Antibiotic Residues in Food Using Surface-Enhanced Raman Spectroscopy

Jiayi Ji

College of Chemistry, Tianjin Normal University, Tianjin, China
1009151753@qq.com

Abstract. The widespread presence of antibiotic residues in food constitutes a serious and escalating threat to public health. The overuse of antibiotics in animal husbandry and agriculture can lead to bioaccumulation in meat, dairy products, and crops, potentially contributing to the development of antimicrobial resistance in humans. Therefore, developing accurate, efficient, and on-site methods for detecting trace levels of such contaminants is of paramount importance. Surface-enhanced Raman spectroscopy (SERS) has emerged as a powerful analytical tool for this purpose, offering exceptional advantages such as ultra-high sensitivity, molecular fingerprint specificity, and capacity for rapid, label-free analysis. This review systematically summarizes the key achievements of SERS technology in the detection of various antibiotic residues across diverse food matrices. It specifically compiles and discusses the achieved limits of detection and recovery rates reported in recent studies, critically evaluating the performance of different SERS substrates and assay formats. The objective is to provide a comprehensive reference for researchers and practitioners, highlighting both the current capabilities and future potential of SERS in ensuring food safety and safeguarding consumer health.

Keywords: Surface-Enhanced Raman Spectroscopy, food contamination, antibiotic residues, efficient detection

1. Introduction

In the field of food safety, antibiotic residues are among the most concerning and sensitive issues to the public. Antibiotics, a class of antimicrobial compounds metabolized by microorganisms or artificially synthesized, were initially used to treat infectious diseases in humans and animals. With the large-scale development of aquaculture, they have gradually been expanded as "multifunctional tools" in livestock and aquatic farming, serving the purposes of treating animal diseases, preventing group infections, and promoting growth [1]. However, the excessive and improper use of antibiotics has gradually transformed them from "health safeguards" into a core cause of animal-derived food contamination, ecological environment damage, and threats to human health.

The hazards of antibiotic residues in animal-derived foods have permeated multiple dimensions of food, environment, and health. For humans, long-term intake of meat, eggs, milk, and other foods containing residual antibiotics can disrupt the balance of intestinal flora, reduce immune function, and induce the emergence of drug-resistant strains (such as "superbugs"). Some antibiotics (like

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aminoglycosides) can directly damage organs such as nerves and kidneys, while tetracyclines can affect the absorption of minerals in the human body. In severe cases, they may even cause allergic reactions, carcinogenicity, teratogenicity, and other toxic effects [2]. For aquaculture, the abuse of antibiotics not only damages organs such as the liver and kidneys of animals, reducing their growth performance and disease resistance but also accelerates the spread of drug-resistant bacteria in the breeding environment, significantly increasing the difficulty of subsequent disease control [3]. More alarmingly, approximately 5%-90% of antibiotics in aquaculture cannot be fully absorbed by animals and are discharged into the environment along with feces and aquaculture wastewater. In the soil around Chinese farms, the residues of tetracycline antibiotics are significantly positively correlated with the abundance of drug-resistant genes. In the water bodies of the Pearl River Delta, the detection rate of sulfonamide-resistant genes exceeds 85%. These pollutants can also return to the human body through the food chain and water cycle, forming a closed-loop hazard chain of "breeding - environment - food - health" [4, 5]. According to statistics, the total consumption of antibiotics in Chinese aquaculture production in 2018 was approximately 29,800 tons, with an average of 140 grams of antibiotics used per ton of animal-derived food produced, far higher than the level in developed countries [6]. The abuse of antibiotics has become a common problem across multiple fields.

To control the risks of antibiotic residues, various existing detection technologies have been developed, but all have obvious limitations. Microbiological methods are only suitable for the preliminary screening of large batches of samples, unable to achieve accurate quantification of trace residues and easily interfered by other pharmaceutical ingredients. Immunoassays, although highly sensitive, involve cumbersome sample pretreatment processes and high detection costs, making them difficult to apply to the rapid detection of unknown or large batches of samples. Chromatography-mass spectrometry, while capable of accurate qualitative and quantitative analysis of residual antibiotics, is complex to operate, expensive in equipment, and poor in portability, failing to meet the needs of on-site immediate detection in farms and food processing sites [7]. Emerging sensor technologies, despite their advantage of simple operation, still require further optimization in terms of detection accuracy and stability. Therefore, the development of a detection technology with the characteristics of rapidity, sensitivity, and portability is crucial for the efficient and regular control of antibiotic residues in animal-derived foods.

Surface-Enhanced Raman Spectroscopy (SERS) technology, with its ultra-high detection sensitivity, fast analysis speed, and suitability for on-site detection, provides a new technical direction to solve this problem. This paper focuses on the application of SERS technology in the detection of antibiotic residues in animal-derived foods, systematically sorting out its enhancement mechanism, detection methods for typical antibiotics (such as tetracyclines and aminoglycosides), and discussing its application potential and development trends in actual food detection scenarios.

2. Enhancement mechanism of surface-enhanced Raman spectroscopy (SERS)

The core of SERS technology lies in achieving significant amplification of Raman signals through specific substrates. Its enhancement effect mainly stems from the synergistic action of electromagnetic enhancement (physical mechanism) and chemical enhancement (chemical mechanism), which together determine the detection sensitivity and signal characteristics of SERS (Figure 1) [8].

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2.1. Electromagnetic enhancement mechanism

Electromagnetic enhancement is the primary contributor to the amplification of SERS signals, with its core rooted in the plasmon resonance effect on the surface of metal substrates. When incident light irradiates noble metal nanostructures (such as nanoparticles and nanorods) like gold and silver, the free electrons on the metal surface oscillate collectively at the frequency of the electromagnetic field, forming surface plasmon resonance (SPR). When the resonance frequency matches the frequency of the incident light, an extremely strong local electromagnetic field (i.e., "hot spots") is generated on the metal surface. At this point, the Raman scattering signals of molecules adsorbed in the "hot spot" regions can be amplified by a factor of 10^6-10^{10} [8].

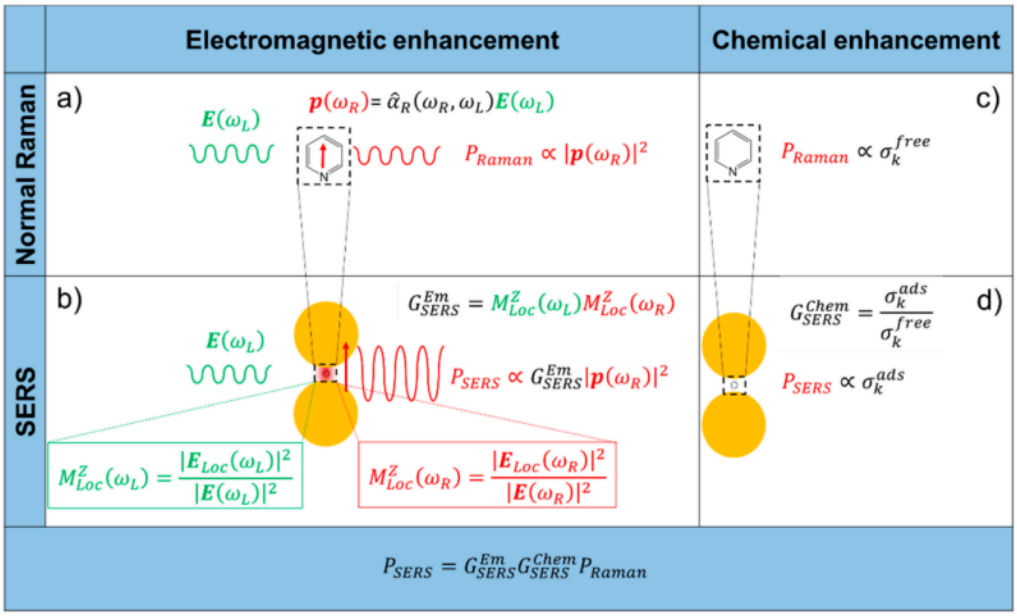

Figure 1. Schematic diagram of electromagnetic enhancement and chemical enhancement mechanisms [8]

This enhancement is closely related to the type of metal, as well as the shape, size, and spacing of nanostructures. For instance, the SPR peak of silver nanoparticles lies in the visible to near-infrared region, exhibiting a more significant enhancement effect on the Raman scattering of most molecules. In contrast, although the SPR peak of gold nanoparticles is redshifted, they possess better chemical stability, making them suitable for detection in complex systems [8].

2.2. Chemical enhancement mechanism

Chemical enhancement arises from charge transfer between molecules and the metal substrate, with an enhancement factor typically ranging from 10^2 to 10^3. Its mechanism can be divided into "static chemical enhancement" and "dynamic chemical enhancement". Static chemical enhancement refers to the adsorption of molecules on the metal surface through chemical bonds (such as Au-S bonds), which changes the electron cloud density distribution of the molecules, leading to enhanced Raman activity of specific chemical bonds. Dynamic chemical enhancement occurs at the moment of laser excitation, where a transient charge transfer takes place between the molecule and the metal,

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forming an excited-state charge transfer complex, which significantly increases the change in the polarizability of the molecule (Figure 2) [9].

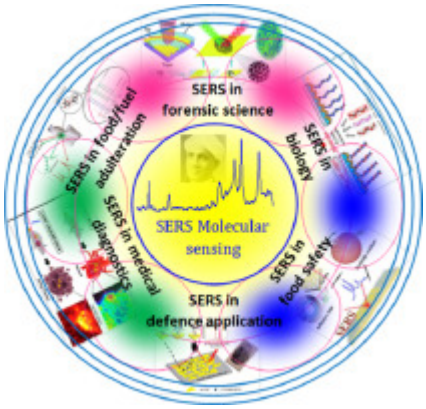

Figure 2. Schematic diagram of charge transfer and SERS signal enhancement pathways [9]

Chemical enhancement has strong specificity. For example, molecules containing heteroatoms such as nitrogen and sulfur are prone to form coordination bonds with metals, and their chemical enhancement effect is more significant than that of molecules without heteroatoms. This provides a theoretical basis for the targeted detection of molecules with specific functional groups [9].

2.3. Regulation of SERS substrates on enhancement mechanisms

SERS substrates are the core carriers for achieving enhancement effects. Their material selection, structural design, and preparation processes directly affect the synergistic effect of electromagnetic enhancement and chemical enhancement [10].

2.3.1. Selection of substrate materials

Commonly used substrate materials include alkali metals, transition metals, noble metals, and graphene. Among these, noble metals (gold, silver) have become the most widely studied and offer the best enhancement effects, thanks to their excellent plasmon resonance properties. Their surface plasmon oscillations can strongly amplify local electromagnetic fields when excited by light, which significantly boosts the Raman signals of adsorbed molecules—making them the preferred choice for SERS substrate fabrication [10]. For example, silver substrates, whose resonance frequency matches the visible light range, can efficiently trigger electromagnetic enhancement. In contrast, gold substrates, with superior chemical stability, are more suitable for detecting complex food samples [9].

2.3.2. Development and preparation technologies of substrates

The preparation of SERS substrates has gone through four stages: starting from the early "surface-roughened substrates" prepared by vacuum deposition and electrochemical redox cycling, to "micron-scale sol-gel particles" fabricated via laser melting and wet-chemical synthesis, and further to "precision-structured substrates" based on nanotechnology [10]. Current nanomanufacturing technologies (such as electron beam lithography, nanosphere lithography, etc.) can precisely regulate the "hot spot" distribution and surface structure of substrates, effectively improving the uniformity and reproducibility of enhancement effects [9].

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2.3.3. Evaluation criteria for high-quality substrates

An ideal substrate must meet multiple requirements: high enhancement effect to ensure sensitivity, high signal reproducibility and uniformity to improve reliability, high stability to extend service life, as well as simple preparation process and low cost to enhance practicality. For example, the self-assembled Ti_3C_2Tx@Au nanoparticle film substrate, combined with phytic acid capture molecules, not only improves sensitivity through the electromagnetic enhancement of noble metals but also enhances specificity by utilizing the charge transfer between molecules and the substrate, enabling highly sensitive detection of antibiotic-resistant bacteria [11].

In summary, the enhancement effect of SERS is the result of the synergy between electromagnetic enhancement and chemical enhancement, while the material, structure and preparation process of the substrate are key to regulating the enhancement effect. This mechanistic characteristic endows SERS with both ultra-high sensitivity and molecular specificity, providing a core technical basis for the rapid detection of low-concentration antibiotic residues in animal-derived foods.

III. Research Progress

At present, surface-enhanced Raman scattering (SERS) has become a research hotspot in the field of antibiotic residue detection, with characteristics such as high sensitivity, rapid response, and non-destructive detection [12], It shows wide applicability in antibiotic detection across multiple scenarios such as food and environment. It can achieve accurate identification of trace antibiotics in complex matrices, avoiding the time-consuming and cumbersome operation defects of traditional detection methods, and also providing efficient technical support for high-throughput screening of various antibiotics.

3. Application of SERS technology

3.1. Application of SERS technology in tetracycline detection: Analysis of materials and performance based on two types of substrates

As a widely used antibiotic, the detection of tetracycline (TC-HCl) residues is of great significance to food safety and environmental monitoring. SERS technology provides an effective approach for its trace analysis by virtue of high sensitivity.

3.1.1. TiO_2NTAs/Ag composite substrate

As shown in Figure 3, Zhang et al. proposed a two-step method of "anodic oxidation + photoreduction" to construct a TiO_2NTAs/Ag composite substrate: first, ordered TiO_2 nanotube arrays (TiO_2NTAs) were prepared by anodic oxidation, and after annealing at 450 ℃ , Ag nanoparticles were modified on the surface by photoreduction to form a composite substrate with uniform structure [13].

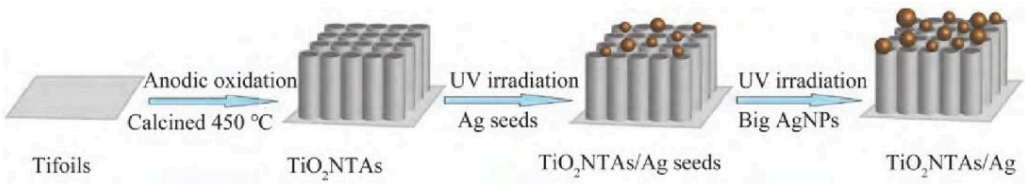

Figure 3. Schematic diagram of TiO_2NTAs/Ag assembly [13]

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The TiO_2 nanotubes of this substrate (with a diameter of approximately 50 nm and a length of 3.3 μm) can enrich tetracycline molecules through structural confinement (as shown in Figure 4). The Ag nanoparticles (with a size concentrated at 150 nm) amplify the Raman signal by virtue of localized surface plasmon resonance. Under the synergistic effect of the two, the substrate can achieve stable response to tetracycline in the concentration range of 5 ng/L to 500 μg/L, with a detection limit as low as 4.809×10^{-3} ng/L. Moreover, the signal shows no obvious attenuation after 8 cycles of use and 30 days of storage.Spectral analysis reveals that the characteristic peaks of tetracycline undergo significant changes on the surface of this substrate. For example, the amide bond vibration peak at 1616 cm^{-1} shifts to 1602 cm^{-1}, and new cycloalkene vibration peaks such as the one at 920 cm^{-1} appear, providing a clear basis for qualitative analysis (as shown in Figure 5) [13].

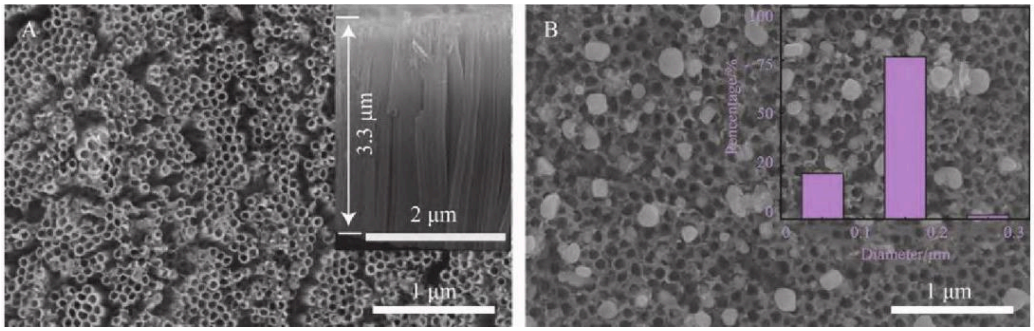

Figure 4. SEM images of TiO_2NTAs and TiO_2NTAs/Ag [13]

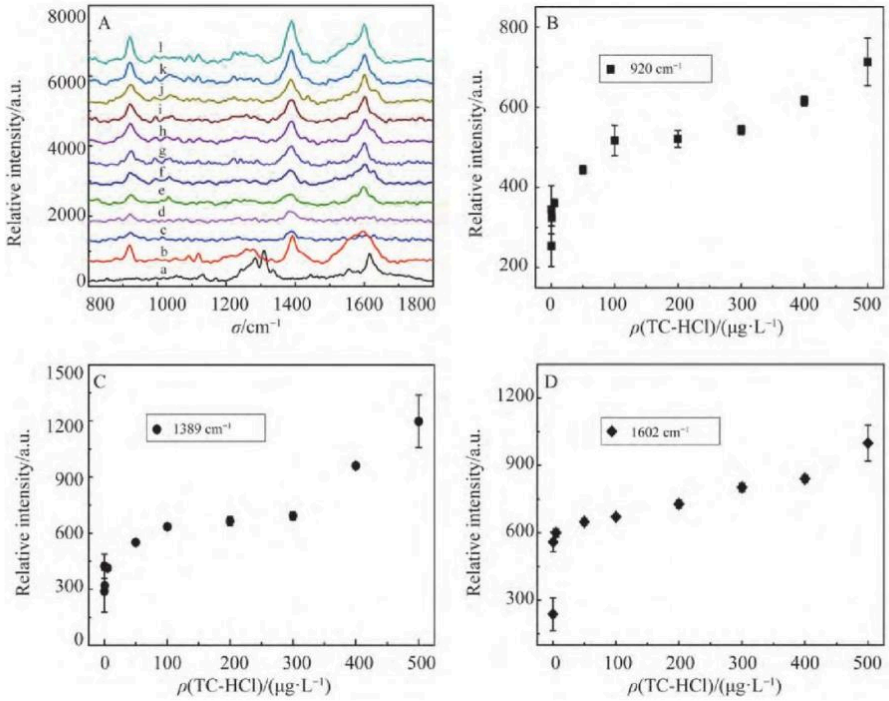

Figure 5. SERS spectra and concentration scatter plot [13]

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3.1.2. Commercial OTR202+OTR103 substrate

In the practical application of tetracycline detection, some studies have also adopted commercial reagents to construct rapid detection systems. Zhao Jinhui et al. used OTR202 and OTR103 as enhancement reagents, and the detection could be carried out by simply mixing the reagents with tetracycline solution, without complex substrate synthesis steps (as shown in Figure 6) [14].

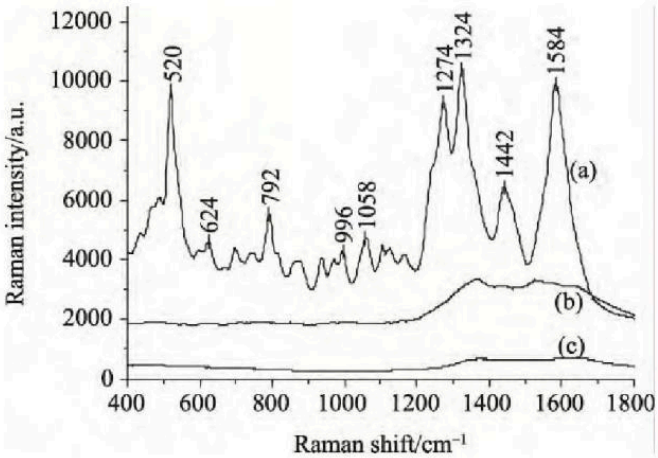

Figure 6. Raman spectra of tetracycline aqueous solution [14]

In this system, the enhancement effect of the reagents makes the tetracycline aqueous solution, which originally has no obvious Raman signal, show characteristic peaks. After deducting the fluorescence background by the air-PLS method, the signal clarity is further improved. A standard curve with a linear correlation coefficient r = 0.9897 is established in the concentration range of 0.1~20 mg/L (as shown in Figure 7). The characteristic peaks are concentrated at 1584, 1442, 1274 cm^{-1} and other positions, among which the 1274 cm^{-1} peak can be used as the basis for quantitative analysis.

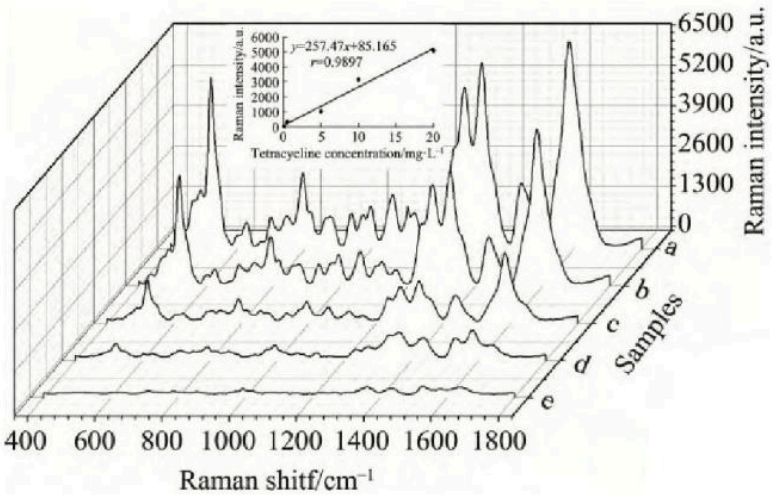

Figure 7. SERS spectra of tetracycline aqueous solutions with different concentrations [14]

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3.2. Application of SERS technology in the detection of aminoglycoside antibiotics

Peng et al. synthesized gold colloid nanoparticles by reducing chloroauric acid with trisodium citrate using an induction cooker heating method, and employed them as SERS enhancement substrates. The Raman enhancement effect of this substrate is closely related to the particle size: as the amount of trisodium citrate added is adjusted, the particle size of the gold colloid gradually decreases. Among them, the gold colloid with a particle size of approximately 80 nm exhibits the optimal enhancement effect on 15 mg/L STR aqueous solution due to the compatibility of particle spacing and charge distribution—after mixing, STR shows obvious Raman peaks at 838, 970, 1031 cm^{-1} and other positions, while there are no significant signals in the single STR aqueous solution or gold colloid alone (Figure 8 and Figure 9) [15].

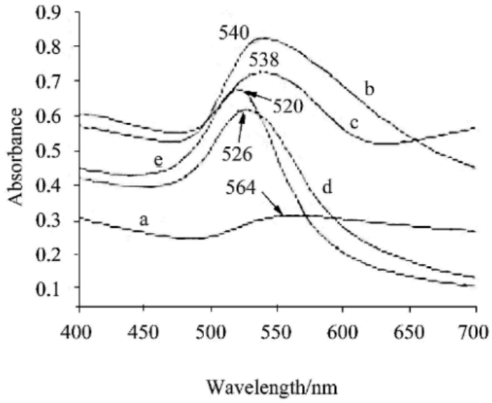

Figure 8. UV absorption spectra of gold colloid nanoparticles [15]

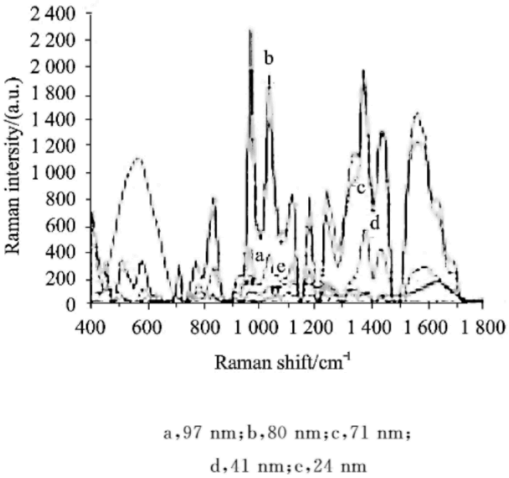

Figure 9. SERS of STR aqueous solution under the conditions of Au colloid nanoparticles with different particle sizes [15]

By optimizing the excitation power (700 mW), the amount of gold colloid added (500 μL) and the adsorption time (1 min), the enhancement stability of the system is further improved: in the concentration range of 2.0~20.0 mg/L, the mass concentration of STR shows a good linear relationship with the Raman peak intensity at 1031 cm^{-1}, and the linear equation is Y=293.31X+435.42. In terms of peak identification, 1031 cm^{-1} corresponds to the C-C stretching

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vibration of the pyranose ring, 970 cm^{-1} is attributed to the O-H and C-H bending vibrations of the pyranose ring, and 838 cm^{-1} corresponds to the ring vibration of the furanose ring. These characteristic peaks provide a clear basis for the qualitative analysis of STR. In the detection of actual water samples, the recovery rate of this method reaches 92.1%~133.0%, and the relative standard deviation is less than 2.41% (as shown in Figure 10).

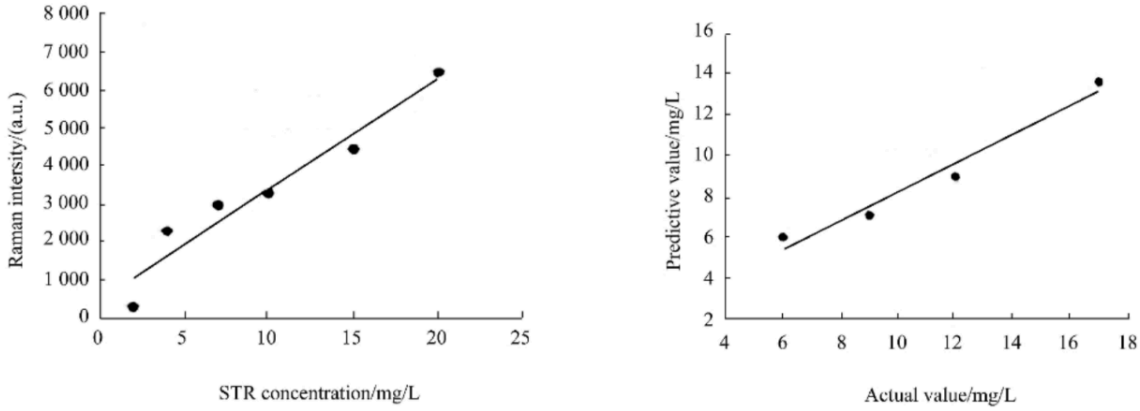

Figure 10. Working curve of STR aqueous solution and relationship diagram with prediction set samples [15]

3.3. Application of SERS technology in the detection of penicillin antibiotics: Substrate optimization and residue analysis with NAF as an example

Nafcillin (NAF), a commonly used veterinary penicillin drug, its residues in duck meat and other animal-derived foods may pose threats to health through the food chain. SERS technology, with its characteristics of high sensitivity and rapid analysis, has become one of the suitable technologies for the detection of such residues.

In the screening and regulation stage of SERS-active substrates, the study compared the enhancement effects of two types of gold nanocolloids and one type of silver nanocolloid, and finally determined gold nanocolloid A as the optimal substrate. The gold nanocolloid prepared by induction cooker heating with 0.7 mL of 1% sodium citrate as the reducing agent can efficiently adsorb NAF molecules and form "hot spots" due to its uniform particle size distribution and suitable surface roughness, enabling NAF to exhibit clear Raman peaks at 521, 815, 1240 cm^{-1} and other positions. Meanwhile, the fluorescence interference was deleted by adaptive iterative penalized least squares method, and sodium chloride was used as the activator to clarify the attribution of characteristic peaks of NAF: 521 cm^{-1} corresponds to N-H bending vibration and naphthyl α-substitution; 815 cm^{-1} is associated with in-plane deformation vibration of β-lactam group; 1367 cm^{-1} corresponds to C-H bending and naphthyl skeleton vibration (Figure 11) [16].

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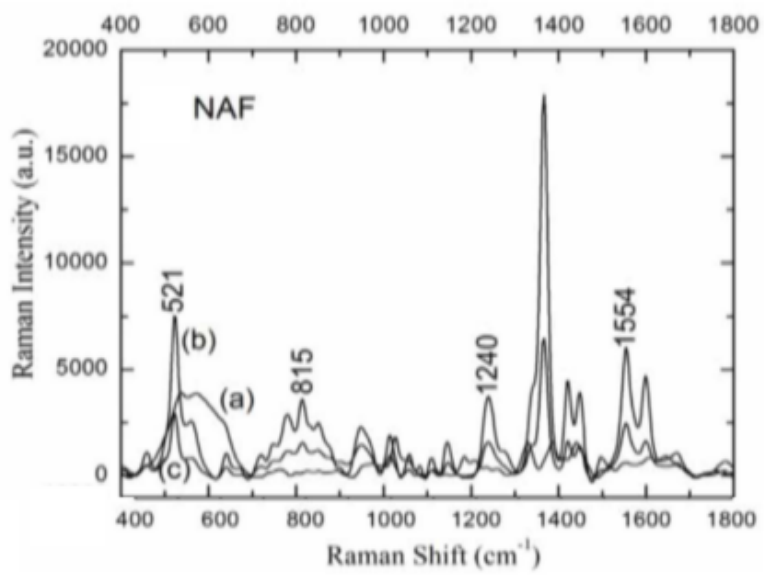

Figure 11. Effects of different nano-sols on SERS signals of NAF aqueous solution [16]

To address the interference issue from duck meat matrix, the extraction effects of acetonitrile and ethyl acetate were compared, and ethyl acetate was selected as the extraction solvent. As shown in Figure 12, The SERS peak intensity and quantity of NAF samples extracted by this solvent were more prominent, and the blank duck meat solution showed no interference at characteristic peak positions such as 521 and 1449 cm^{-1}. In the quantitative analysis, using the ratio of peak intensities at 460 cm^{-1} and 521 cm^{-1} as the index, a calibration curve equation y=0.6215x+1.2491 (R^2=0.9541) was established in the concentration range of 0.2~10.0 mg/L. The average recovery rate of actual sample detection reached 103~116%, verifying the reliability of the method.

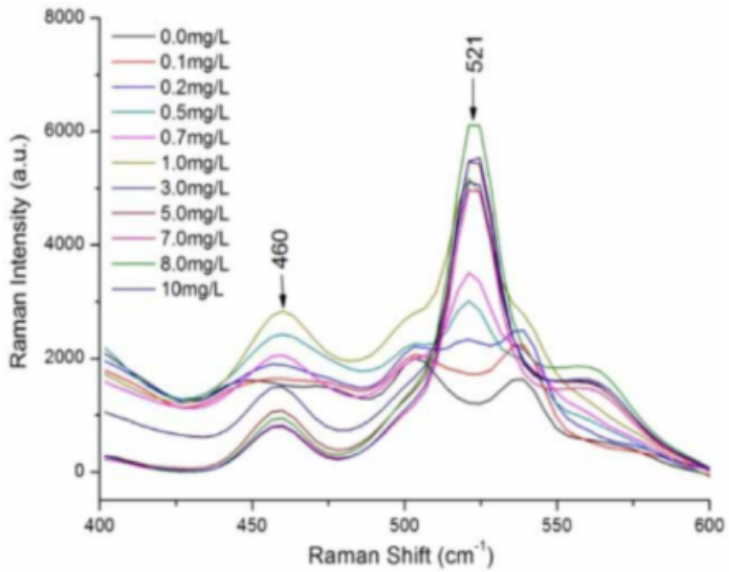

Figure 12. SERS spectra of NAF at different concentrations [16]

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This detection logic is consistent with the surface-enhanced Raman spectroscopy (SERS) analysis approach for penicillin degradation products. Both achieve efficient detection of trace residues through substrate optimization and accurate identification of characteristic peaks [17].

4. Conclusion and outlook

This study focuses on the application of SERS technology in the detection of antibiotic residues in food, clarifying that its core enhancement mechanism lies in the synergistic effect of electromagnetic and chemical enhancement, while the material selection and preparation process of the substrate are key to regulating the enhancement effect. Through detection practices on typical antibiotics such as tetracyclines, aminoglycosides, and penicillins, the adaptability of SERS technology in the detection of different types of antibiotics has been verified—it not only achieves accurate identification of trace target analytes but also adapts to the detection needs of complex food samples through substrate optimization and matrix interference elimination, demonstrating the technical advantages of high sensitivity and rapid analysis.

In the future, the development of SERS technology needs to further break through existing limitations: on the one hand, it is necessary to improve the multi-component adaptability and stability of the substrate, and develop composite functional substrates that can simultaneously detect multiple types of antibiotics; on the other hand, it is required to promote the integration and portability of detection systems, combining microfluidics with small spectral equipment to adapt to on-site real-time detection scenarios. At the same time, it is also necessary to expand the universality of detection methods, optimize processes for more food matrices, and promote SERS to become a standardized technical means for food safety control through multi-technology combination and practical scenario verification, so as to provide more efficient support for food quality and safety.

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