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Application of SERS quantitative analysis method in food safety detection

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Abstract: Food safety and quality have gained much attention and the capability to evaluate food quality and safety in a sensitive, rapid, and reliable manner is of great importance in the food industry. Surface-enhanced Raman scattering (SERS) with the advantages of excellent sensitivity, high selectivity, non-destructive nature, and significant enhancement to identify the target has demonstrated a great potential for quick detection of the food sample. The enhancement of Raman signals for SERS is not only related to the interactions between substrates and samples but also the functionalization of substrates to gain SERS active substrates. In the present review, this paper summarized the progress of SERS quantitative analysis and application in food safety detection. The future trends and perspectives were also given.

Keywords: surface enhanced Raman scattering, food safety, application

1 Introduction

In recent years, vibrational spectroscopy such as Raman spectroscopy has been widely used to detect pesticide residues, biotoxins, antibiotics, and pathogens in food due to its high sensitivity and rapid, trace detection features. SERS is a highly sensitive elastic scattering method that uses ordinary Raman scattering to detect the surface of a sample adsorbed with coarse nanoparticles (such as gold, silver, or copper), resulting in a stronger Raman signal for the sample to be measured, specifically by a factor of 10^3-10^6 [1]. SERS technology is widely used in environmental monitoring [2], explosives detection [3], biomedical [4], food safety [5], and pesticide detection [6] due to its high sensitivity, trace level, fast response, and details about the characterization of the "fingerprint". For example, Huang et al. successfully prepared snowflake-like gold nanoparticles used as SERS substrates, and the results showed that the snowflake-like Au NPs substrates have excellent SERS activity with a detection limit of about 3×10^{-9} mol·L^{-1} in aqueous solution of rhodamine 6G and 1×10^{-8} mol·L^{-1} for organophosphorus pesticides in solution [7]. Ilhan et al. developed a paper-based SERS platform and an immunomagnetic enrichment assay for the specific detection of *Escherichia coli* in milk, and the SERS results obtained were consistent with conventional plate colony counting methods [8]. SERS can even reach the level of single-molecule detection under the near-infrared laser, so it has a great prospect of application in food quality and safety evaluation. The purpose of this review is to introduce the theoretical basis of SERS, SERS active substrates, SERS detection techniques, and the application of SERS in food safety evaluation, and to analyze the current challenges and prospects of SERS technology in the field of food safety detection. Based on the previous summary, this review mainly focuses on the application of SERS technology in recent years and summarizes the SERS detection technology. Finally, it summarizes the current challenges and potential future trends of SERS technology, hoping to provide readers with a good understanding of the latest applications of SERS technology and encourage more applications of SERS for food safety evaluation.

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2 Theoretical bases of SERS

Raman spectroscopy is an inelastic scattering of an incident photon with a molecule, discovered by C.V. Raman in 1928, which allows the analysis of scattering spectra at frequencies different from the incident light to obtain information about the vibration and rotation of molecules and is applied to the study of molecular structure. Raman scattering involves only small energy changes, and typical Raman scattering cross sections are small, with values of about 10^{-29} cm^2/sr [9], 10 orders of magnitude lower than those of infrared or fluorescence spectroscopy, making typical Raman spectroscopy too weak to be used for trace detection in routine analysis, which also makes Raman spectroscopy a great challenge for trace detection [10]. Due to the general weakness of Raman scattering (typically one millionth of the incident light frequency) [11], only solid samples or biological samples with high concentrations of aqueous solutions show good Raman scattering, but when nanometer roughness metals (such as gold and silver) are adsorbed on the sample surface, the Raman signal of the sample is significantly enhanced, allowing the detection of samples at very low levels (picomolar to femtomolar concentrations), also known as SERS [12].

Although SERS technology has undergone more than 40 years of development, there is still no definite conclusion on the enhancement mechanism, and it is now generally accepted in academic circles that the main mechanisms of SERS are physical enhancement mechanism (EM) and chemical enhancement mechanism (CT), and the result of the joint action of the two classical mechanisms [13]. EM mechanism is the mechanism of EM field enhancement. The reason for the enhancement is that when the EM wave interacts with the metal surface, if the metal surface is rough, then the EM wave will excite a local surface plasma on the surface, which leads to the amplification of the electric field near the surface. Surface plasma is the collective oscillation of free electrons in a metal under a photoelectric field, and the local electromagnetic field enhancement caused by surface plasmon resonance (SPR) is also considered to be the main core of SERS enhancement [14]. The electromagnetic enhancement mechanism is a purely physical description of the local electromagnetic field enhancement caused by plasma resonance on the surface of metallic nanoparticles, which has been confirmed by many scholars at home and abroad. Unlike the physical enhancement mechanism, the chemical enhancement mechanism mainly considers the charge transfer interactions between the metal nanoparticles and the sample, that is the charge transfer between the chemical bonding, surface complexes, light-induced and the substrate, which is generally in the range of $10\text{-}10^3$, and the enhancement effect is much lower than the physical enhancement [13]. Due to the differences between the molecules and their interactions with metal nanoparticles, the chemical enhancement mechanism is not universal compared to the physical enhancement mechanism. Although the mechanism of SERS enhancement is not conclusive, SERS is widely used due to its high sensitivity, fast response, and "fingerprint" recognition features. In addition to these features, the good compatibility with water systems and the linear relationship between spectral intensity and analytical concentration determines that SERS technology can be used for qualitative [15], semi-quantitative [16], and quantitative analysis [17].

3 SERS-active substrates

As can be seen above, the SERS phenomenon is relatively complex, and there is no uniform substrate to detect all target analytes, so it is necessary to develop different high-sensitivity SERS substrates to cope with a variety of analytes, making SERS technology a powerful tool to detect specific target molecules at trace levels. In recent years, with the continuous development of nanotechnology, different shapes, sizes, compositions, and spatial distances of SERS substrates have been developed, because the shape, size, and composition of the substrates can affect the sensitivity of SERS detection, and they can generate different enhancement factors (EFS) to enhance SERS to different degrees [18].The enhancement factor is often used to reflect the activity of the substrate and the sensitivity of SERS is greatly influenced by the "hot spots", which are the largest electric field enhancement sites on metal nanoparticles, mainly in the tiny gaps between the metal nanoparticles [19]. Due to the occurrence of localized surface plasmon resonance (LSPR) of the metal nanoparticles, the electric field of the metal surface part is significantly enhanced, showing a good Raman signal. Therefore, the enhanced Raman signal is not only related to the interaction between the substrate and analyte, but also to the functionalization of the substrate to obtain a better substrate activity [20]. For food quality evaluation, it is particularly important to select functionalized substrates for more accurate detection of target analytes. The common active substrates for SERS in recent years are divided into metallic nanomaterials (noble metals and transition metals) and non-metallic

nanomaterials (graphene, semiconductors, etc.) [21]. For example, Ekmen et al. synthesized surface molecularly imprinted magnetic nanoparticles (MIP@Fe_3O_4NPs) for the sensitive and selective quantification of malachite green in tap water and carp samples through a recently developed active mechanism called reversible chain transfer catalytic polymerization (RTCP) [22]. Wang et al. constructed a highly sensitive SERS substrate based on Ag-nanoplates decorated graphene-sheets for ultrasensitive SERS detection of organic pesticides (including thiram and methyl parathion and their mixtures). The Ag-nanoplates@graphene hybrids (Ag-NP@GH) substrate showed low detection limits of 40 and 600 nM for thiram and methyl parathion, respectively, and more importantly, Ag-NP@GH substrate showed good SERS signal reproducibility with relative signal deviation as low as 5.6% [23]. Guselnikova et al. proposed functionalized surface equipartition oscillator supported gold grating surfaces with metal-organic backbone (MOF-5) for sensitive, selective, and reproducible SERS detection of organophosphorus pesticides, in addition to selective detection and identification of several relevant organic contaminants such as azo dyes and mycotoxins [24]. Gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) were used more often in these studies. There are also nuclear-shell nanoparticles developed on this basis. To enhance the SERS signal, these noble metal nanoparticles are transformed into various shapes, such as nanorods, nanodendrites, nanoflowers, nanosheets, nanomembranes, and nanostars [25,26].

In general, SERS active nanosubstrates can be divided into colloidal nanosubstrates and solid nanosubstrates. Colloidal substrates are easier and more sensitive to make. However, since it is a solution system, it is not easy to control the assembly of metal nanoparticles and evaluate the exact position of the target analyte, so the developed solid nanosubstrates can solve this problem, and the solid substrates have good stability and durability.

3.1 Colloidal substrates

Gold and silver nanoparticles with diameters of 10-200 nm are typically used to make colloidal substrates, which are readily available and inexpensive. Due to its high sensitivity, ease of fabrication, and stability, it is widely used for the detection of pesticide residues, biotoxins, and antibiotics, etc. [27]. In addition to chemical reduction methods, also known as wet synthesis techniques, radiation reduction and laser ablation are used to prepare metalloid substrates, but the most widely used method is chemical reduction. However, due to the more rapid reaction of the reduction method, it is not easy to control the nucleation rate of nanoparticles, which leads to irregular and inhomogeneous size and shape of nanoparticles, and ultimately leads to lower stability and reproducibility of chemical reduction [28]. Therefore, in the following long time, many scholars in China and abroad have tried to improve the SERS strength by improving the shape and size of metal nanoparticles. Bastús et al. used growth kinetics to control the growth rate of metal nanoparticles and prepared gold and silver nanoparticles with high uniformity and adjustable particle size by a stepwise growth method [29]. As mentioned above, the size and shape of metal nanoparticles affect the intensity of SERS through surface plasmon resonance, so the development of nanosubstrates of different sizes and shapes is of great significance for high sensitivity detection. D'Elia et al. fabricated gold nanorods for ultra-trace detection of cocaine in unprepared oral fluid samples, and the results confirmed the increased sensitivity and high stability and reproducibility of the detection with gold nanorods [30]. Wang et al. developed a novel solvothermal method to synthesize Ag nanocubes with controllable size. The PVP was used as the capping agent, ethylene glycol as reducing agent and glycerol as the viscosity regulator in the growth of Ag nanocubes. The results show that Ag nanocubes are highly SERS-active substrates and the detecting limit of thiram can reach as low as 10^{-9} M [31].

Numerous experiments have confirmed that gold nanoparticles have better stability and significantly more controllability than silver nanoparticles, and silver nanoparticles have higher SERS activity than gold nanoparticles. Therefore, many scholars often use the two in combination to obtain more powerful SERS substrates. Pu et al. developed two-dimensional (2D) stable Au-Ag core-shell nanorod (Au@AgNRs) nanoarray substrates with high-performance SERS activity based on an interfacial self-assembly strategy and successfully applied them for the detection of thiram in apple samples. A broad linearity range of 0.01-10 mg/L and a low limit of detection of 0.018 mg/L were achieved for thiram solution. The substrates were stable and showed satisfactory sensitivity with 93-116% recovery after 4 weeks of storage at ambient temperature [32].

On the other hand, electrostatic repulsion exists between the metal nanoparticles in the colloidal matrix system, and the stability of the system is also maintained by electrostatic repulsion, so when testing liquid food, the charge present in the sample will have a great impact on the adsorption ability between the metal nanoparticles and the target, thus leading to a reduction in the reproducibility of the test results. Besides, the pH of the sample

matrix can affect the metal colloidal solution. For a more commercial development of colloidal matrices, improvements in their stability and reproducibility are needed.

3.2 Solid substrates

In order to overcome the poor stability and reproducibility of the colloidal matrix, many immobilization techniques have been developed to adsorb metal nanoparticles onto solid substrates, the most commonly used techniques are nanolithography, microsphere lithography, and self-assembly techniques. In previous studies, self-assembly techniques were found to be more effective and easier to prepare than nanolithography [33]. Self-assembly technology mainly uses the morphological control of surface functional groups and nanostructures to form ordered structures, which can prepare highly dense and orderly and controlled nanoarrays [34]. Zhang et al. developed a simple self-assembly method to fabricate ordered Ag nanofilms, and the results showed excellent SERS enhancement for the detection of methyl parathion with detection limits up to 10^{-7} M [35]. Meanwhile, different homemade solid surface substrates such as graphene-gold film-gold nanorods, graphene-gold nanorods, and gold film-gold nanorods have been developed for the detection of hazardous substances in food. Sivashanmugan et al. arrayed gold nanodots (AuNDs) on thin graphene (GR) layer, which was mainly prepared by chemical vapor deposition, by focused ion beam technique and used rhodamine 6G as a molecular probe. The results showed that the detection limit of rhodamine 6G was as low as 10^{-12} M and the Raman enhancement factor was increased to 10^{8} fold [36]. Due to the increasing popularity of SERS for trace energy level detection, different commercial solid surface SERS substrates have also been developed. These include Q-SERS (USA), P-SERS (USA), Enspectr SERS substrates (Russia), and inkjet printed SERS substrates. These solid substrates are more expensive, but the assay process is simpler and less time-consuming and has been used by many researchers. For example, Liu et al. used Q-SERS solid substrates with gold-coated SERS-active nanosubstrates for SERS measurements. Three pesticides (carbaryl, phosmet, and azinphos-methyl), which are widely used in apples and tomatoes, were selected for the study quantitative and qualitative models. The study showed that SERS could detect 4.51 ppm carbaryl, 6.51 ppm phosmet, and 6.66 ppm azinphos-methyl in apples; 5.35 ppm carbaryl, 2.91 ppm phosmet, and 2.94 ppm azinphos-methyl in tomatoes at 99.86% confidence interval [37].

In addition, flexible solid SERS substrates have been developed for "in-situ" and real-time inspection of irregular surfaces. Therefore, many scholars have made a lot of efforts to develop flexible substrate materials, such as cotton, tape, polymers, and paper [38]. Wu et al. developed a simple and effective SERS tape sensing strategy based on double pyramidal gold nanoparticles (BP-AuNPs), using the tape to collect methyl parathion from the surfaces of cucumbers, apples, and tomatoes by a simple "stick/peel" procedure (Figure 1) [39]. It is clear from practice that the development of soft, adhesive SERS substrates is of great significance for "in-situ" detection and has a very promising application.

Compared with colloidal matrices, the stability and reproducibility of solid matrices have been significantly improved, but the preparation process is relatively more complicated.

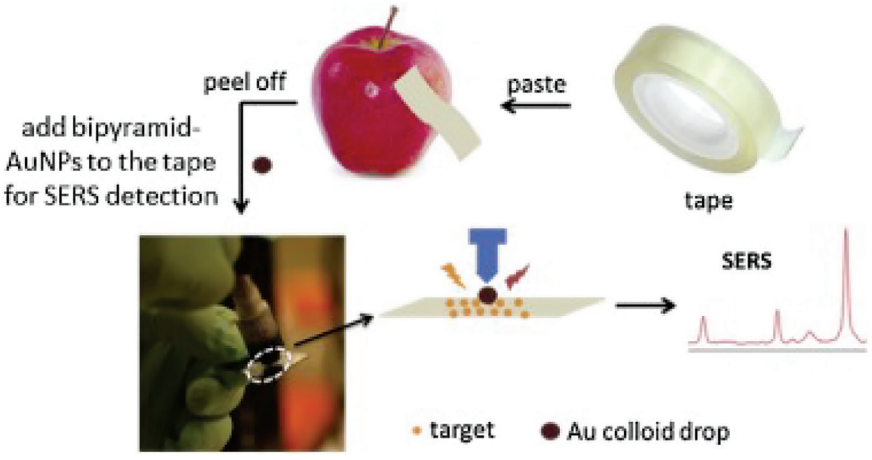

Figure 1: Schematic diagram of BP-AuNPs-based SERS tape sensor for trace sensing on peel surfaces Reprinted with permission from Ref. [39].

4 SERS detection technology

At present, the detection techniques for SERS include label-free SERS detection and labeled SERS detection (Figure 2).

4.1 label-free SERS detection technology

Label-free SERS detection is considered to be the most direct and reliable way to obtain SERS spectra without the need for secondary Raman dyes and synthetic SERS labels (also known as reporter molecules) to obtain a unique "fingerprint" of the target analyte, relying primarily on the interaction between the target analyte and the SERS substrate [40]. In label-free assays, molecular interactions are directly converted into multiple (mechanical, electrical, or optical) signals and can be detected without any labeling. Therefore, label-free SERS assays offer the advantages of simplicity, flexibility, high specificity, and real-time tracking [41]. Hernández et al. developed a low-cost, selective, and reliable gold nanoprism-based label-free nanoadaptor sensor for the detection of trichostatin A (OTA) by SERS. Label-free SERS provides the molecular markers of the aptamer-OTA complex used and can differentiate the OTA solution from 10 to 250 ppb through multivariate analysis [42]. Du et al. synthesized novel multifunctional Fe_3O_4@TiO_2@Ag particles for the immunoassay of prostate-specific antigen (PSA) with a low detection limit of 16.25 pg/mL using a label-free SERS assay [43]. The use of label-free SERS assays for highly sensitive and quantitative determination in food samples remains a challenge. Therefore, the development of a more sensitive and selective SERS detection technique is the focus of many scholars.

4.2 Labeled SERS detection technology

The labeled SERS method is considered as an indirect approach. The method of functionalizing a SERS active substrate with a label and then detecting the SERS signal of that molecule can significantly improve the specificity of a given substance [44]. Labeled SERS detection use external signal tags for analyte measurements. Commonly used tags include electrochemically active molecules, isotopic elements, organic dyes, and nanoparticles [45]. SERS tag-based detection methods have been shown to be very promising for a wide range of detection applications, overcoming the drawbacks mentioned above in Label-free SERS detection. Lu et al. developed a method combining SERS and sandwich-type immunolabel for

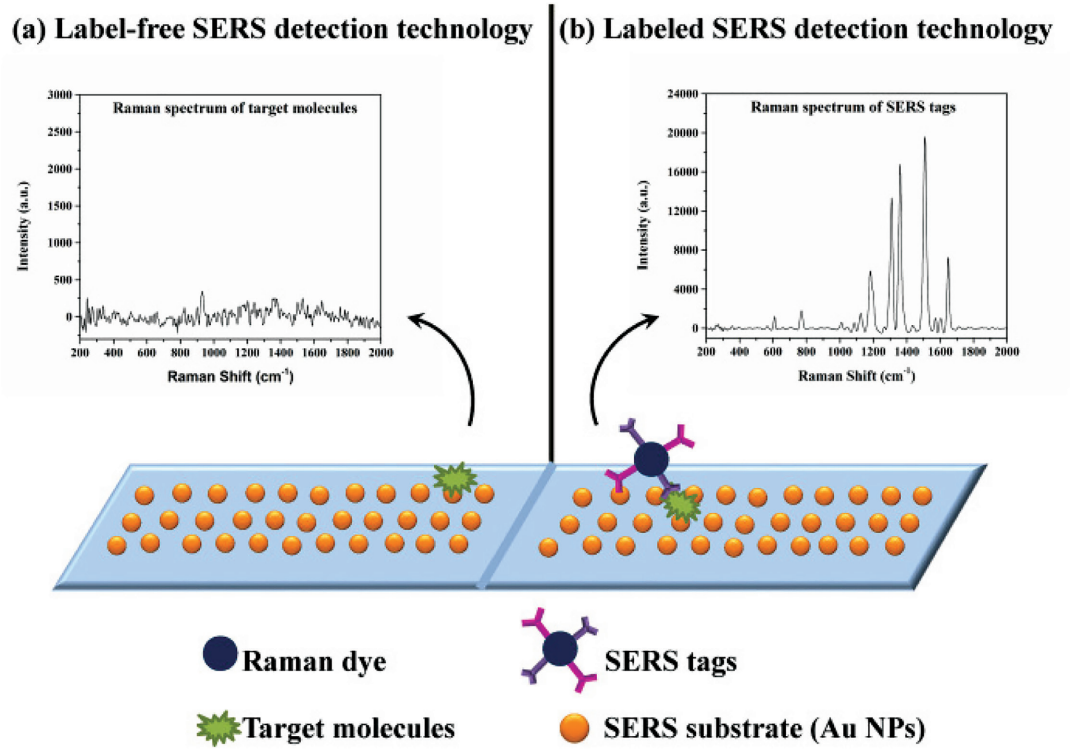

Figure 2: Schematic diagram of (a) label-free SERS detection and (b) labeled SERS detection Reprinted with permission from Ref. [12].

sensitive detection of TYR, in which 4-mercaptobenzyl cyanide is embedded between Au core and Au shell (Au^{4MB}@Au). Core-shell structure is used as SERS label, which is expected to achieve sensitive and quantitative detection of TYR in complex body fluids [46]. Zhang et al. developed a multiple SERS-based lateral flow immunosensor for the identification of six major fungal toxins in maize. Using two characteristic Raman reporter molecules 5,5-dithiobis-2-nitrobenzoic acid (DTNB) and 4-mercaptobenzoic acid labeled synthetic Au@Ag core-shell nanoparticles, the detection limits for zearalenone were 6.2 pg/mL and 0.26 ng/mL for fumonisin B, which are below instrumental analysis and most other biosensors, the limits of detection for zearalenone and fumonisin B were 6.2 pg/mL and 0.26 ng/mL, which are lower than those of instrumental analysis and most other biosensors, and well below the tolerance limits set by the EU, US, and China [47].

5 Application of SERS in food safety detection

5.1 Heavy metal detection

The accumulation and concentration of heavy metals, especially harmful heavy metals, in the human body can cause acute and chronic poisoning. Researchers have done a lot of work on highly sensitive detection of heavy metals in food, as is shown in Table 1.

Song et al. proposed a novel colorimetric/SERS dual-mode detection of the Hg^{2+} method by using SERS-active peroxidase-like Au@AgPt NPs. The dual-mode probe integrated the advantages of facile detection by colorimetric analysis and high-sensitive trace assay by SERS. The limit of detections (LODs) of colorimetric analysis and SERS assay were 0.52 and 0.28 nM, respectively [48].

Table 1: The application of SERS in food safety detection

Classification	Target analyte	SERS substrate	LOD	Reference
Heavy metal pollution	Hg(II)	Au@AgPt NP	0.28 nM	[48,51-53]
		B40/PSS PAH @AuNP	0.5 ppb	
		4,4'-bipyridine (Dpy) to modify silver nanoparticles (AgNPs)	0.1 ppb	
		AuNP@Thiosemicarbazone	79×10^{-8} mol·L^{-1}	
	Cd(II)	B40/PSS PAH@AuNP	0.5 ppb	[51]
	Pb(II)	DNAzymes and enzyme-free CHA amplification system	0.42 pM	[49]
	Cr (VI)	Ag nanoparticles decorated Ag@ZrO_2	0.5 μM	[50]
	As	Au@Ag core-shell nanoparticles	0.1 ppb	[54]
foodborne pathogen	*Staphylococcus aureus*	VAN-Au NPs	1.0×10^{3} cfu·mL^{-1}	[55,58,59,62]
		Fe-MIL-88 was fabricated as artificial enzyme to catalyze leuco malachite green	1.95 cfu·mL^{-1}	
		AuNPs-PDMS	13 cfu·mL^{-1}	
		aptamer-Fe_3O_4@Au MNPs	3 cell·mL^{-1}	
	S. typhimurium	functionalized polymeric magnetic nanoparticles (FPMNPs)	10 cells·mL^{-1}	[56]
	Shigella sonnei	Au@Ag NPs or SiO_2@Au NPs	10 cfu·mL^{-1}	[57]
	Staphylococcus aureus, *Listeria monocytogenes* and *Escherichia coli*	black phosphorus-Au (BP-Au) filter paper	10-10^6 cfu·mL^{-1}	[60]
	E. coli O157:H7	aptamer-4-ATP-GNPs	10^2 cfu·mL^{-1}	[61]
Illegal additives	melamine	Au@HC_3N_4	2.7×10^{-9} M	[63]
		AgNPs/AgNWs	10^{-10} mol·L^{-1}	[66]
	rhodamine B	AuNPs/AgNWs	10^{-15} mol·L^{-1}	[67]
	clenbuterol hydrochloride (CLB)	Fe_3O_4@Au@AgNP	0.003 ng mL^{-1}	[64]
	acid orange II and brilliant blue	Fe_3O_4@Au core–shell	1 μg·mL^{-1},0.5 μg·mL^{-1}	[68]
	formaldehyde	the self-assembled substrates of GNRs were prepared by ethanol modulation	0.86 nM	[65]

(*continued*)

Table 1: (*continued*)

Classification	Target analyte	SERS substrate	LOD	Reference
biotoxin	ochratoxin A (OTA)	Ag@AuCSNPs	0.83 fg·mL^{-1}	[69]
	domoicacid (DA)	animo-AgNPs	0.033 ppb	[72]
	patulin	MIP-SERS	8.5×10^{-11} M	[76]
	aflatoxin B1	aptamer-SERS sensing chip	0.4 fg·mL^{-1}	[73]
	Yersinia pestis, *Francisella tularensis*, and *Bacillus anthracis*	SERS-based LFA	43.4 cfu·mL^{-1}, 45.8 cfu·mL^{-1}, 357 cfu·mL^{-1}	[74]
	tetrodotoxin (TTX)	Fe_3O_4/SiO_2/Au–Ab	0.01 μg·mL^{-1}	[71]
	tropane alkaloids (TAs): scopolamine hydrobromide (SH),methscopolamine bromide (MB) and scopolamine butylbromide (SB)	Ag NPs	10.0 μg·L^{-1}, 1.0 μg·L^{-1}, 1.0 μg·L^{-1}	[70]
pesticide residues	2,4-dichlorophenoxyacetic acid (2,4-D)	hollow Au@Ag bimetallic nanoflowers	0.11 ng·mL^{-1}	[76]
	4-aminothiophenol, methomyl	silver nanoparticle-bacterial nanocellulose paper	3.6×10^{-7} M	[77]
	thiabendazole	Silver colloids synthesized by reduction of $AgNO_3$ by trisodium citrate	4 ppm	[78]
	crystalviolet (CV), thiram	Ag NPs/PDMS	1×10^{-7}M,1×10^{-5}M	[79]
	thiram (TMTD), methyl parathion (MPT), malachite green (MG)	gecko-inspired nanotentacle surface-enhanced Raman spectroscopy (G-SERS)	0.0012 mg·kg^{-1}, 0.02 mg·kg^{-1}, 0.0003 mg·kg^{-1}	[80]
	thiabendazole standard solution, thiabendazole	gold nanoparticles were physically immobilized on the UF	0.01μg·mL^{-1}, 0.125 μg·mL^{-1}	[81]
	thiabendazole (TBZ)	CNF-AgNP	5 ppm	[82]
Residues of veterinary drug detection	thiabendazole, ferbam	Au@Ag-TGANPs	0.12 ppm, 0.003 ppm	[83]
	marbofloxacin	β-cyclodextrin-modified silver nanoparticles (β-CD-AgNPs)	1.7 nmol·L^{-1}	[84]
	thiram, thiabendazole, malachite green, enrofloxacin	Ag/Nanocellulose fibers	0.05 ppm, 0.09 ppm, 0.0014 ppm, 0.069 ppm	[85]
	amantadine	the flower-like gold nanoparticles (AuNFs)	0.005 ng·mL^{-1}	[86]
	fipronil	SiO_2@Au nanoparticles	10^{-7} M	[87]
	kanamycin	2-mercaptobenzothiazole (MBT) labeled Au@Ag core–shell nanoparticles	2 pg·mL^{-1}	[88]
	malachite green (MG)	glass fiber paper modified with AgNPs	5×10^{-10} mol·L^{-1}	[89]

Researchers have also developed a novel "signal-on" SERS sensing platform for Pb^{2+}, which was developed based on CHA amplification and DNAzymes. The biosensor is based on the excellent performance of Pb^{2+}-specific DNAzymes and enzyme-free CHA amplification system. The linear detection range of Pb^{2+} was 1 pM to 100 nM, and the detection limit was 0.42 pM [49]. Moreover, Li et al. designed an Ag nanoparticle decorated Ag@ZrO_2 for SERS to detect Cr (VI). Ag@ZrO_2@Ag nanospheres were used as SERS substrates to sense Cr (VI) in the water at different concentrations, and the linear correlation between SERS intensity and Cr (VI) concentration was R^2 = 0.97 with a detection limit of 0.5 μM [50].

In another study, Mukherji et al. developed the detection of metal ions (Hg^{2+}, Cd^{2+}) added to deionized and tap water using *E. coli* B40 as bioreceptor with a detection limit of 0.5 ppb [51]. In addition, Dou et al. prepared a SERS-based capillary sensor for the detection of mercury

ions (Hg^{2+}) in water using 4,4'-bipyridine (Dpy) functionalized silver nanoparticles with LOD of 0.1 ppb [52]. Also, de Souza et al. developed AuNP@thiosemicarbazone as a substrate for the selective detection of Hg^{2+} with LOD of 79×10^{-8} mol·L^{-1}[53]. Moreover, Zhou et al. proposed a novel type of sensor for detecting As, combining arsenic aptamer with Au@Ag NPs, and measuring the actual concentration of arsenic (III) in the lake water [54].

5.2 Foodborne pathogens detection

Pathogenic bacteria directly or indirectly contaminate food and water sources, and oral infection in humans can lead to intestinal infections, food poisoning, and epidemics of infectious diseases in livestock and poultry.

Liu et al. modified the design of Fe-MIL-88 enzyme to catalyze colorless malachite green to malachite green. Milk and chicken meat were selected as actual samples to evaluate the performance of the *Staphylococcus aureus* (ATCC 29213) detection system by detecting the MG signal and quantifying *S. aureus* in the range of 10^{1}-10^{6} CFU·mL^{-1} with a detection limit of 1.95 CFU·mL^{-1} [55]. Compared with the traditional enzyme-linked immunosorbent assay, the 5,5′-dithiobis (succinimidyl-2-nitrobenzoate) (DSNB)-based SERS immunosensor developed by this method is very sensitive, even in the presence of cross-contamination[56]. In addition, Wu et al. constructed an aptamer-based sensor by synthesizing metal complex-linked gold nanoparticle dimer, which AuNP dimer has the dual function of active substrate and Raman reporter molecule and modified the aptamer against *Shigella sonnei* onto the surface of this bifunctional material. The method achieved recoveries of 92.6-103.8% with LOD of 10 CFU·mL^{-1} [57].

In another study, Zhao et al. constructed a new sandwich LFA format to use VAN and pig IgG for the detection of *Staphylococcus aureus* with a detection limit of 1.0×10^{3} CFU·mL^{-1} [58]. Zhu et al. synthesized hollow Au@Ag NFs SERS aptamer sensors to detect *S. aureus* with LOD of 13 CFU·mL^{-1} [59]. Besides, Huang et al. invented a 3D SERS substrate based on BP-Au filter paper that can specifically identify and differentiate *Staphylococcus aureus*, *Listeria monocytogenes*, and *E. coli* [60]. Some researchers also used aptamer-4-ATP-GNPs to detect *E. coli* O157:H7 sensitively and highly specifically, with LOD value of 10^{2} CFU·mL^{-1}, and a recovery rate of 99-113% [61]. Also, Pang et al. designed a dual identification SERS biosensor for pathogen detection. The recovery rate of *Staphylococcus aureus* for actual samples is 95.0-106.4%, and the relative standard deviation (RSD) is less than 5.3% [62].

5.3 Illegal additives detection

Frequently exposed food safety incidents seriously threatened residents' health and affected public trust in food safety. Tang et al. synthesized holey g-C_3N_4 embedded with Au nanoparticles, and this holey structure of high-density Au nanoparticles also inhibited their own aggregation. The detection limit of crystal violet is 2.7×10^{-9} M, the enhancement factor (EF) is 6.8×10^{5}. The milk samples tested by this method showed a good linear range of 1×10^{-4}-5×10^{-7} M (R^2 = 0.986) and 1×10^{-3}-5×10^{-6} M (R^2 = 0.971) [63]. In another study, Duan et al. synthesized Fe_3O_4@Au@Ag nanoparticles with strong SERS enhancement were as active substrates. The aptamer against clenbuterol hydrochloride (CLB) was immobilized on the surface of the substrate to form a capture probe. The detection limit was 0.003 ng·mL^{-1} [64]. Yan et al. synthesized gold nanorods (GNRs) through a seed growth method to prepare self-assembled substrates by ethanol regulation. The detection limit of HCHO was 0.86 nM, and the EF was 3.9×10^{7}. The relative standard deviation (RSD) in the detection of rice noodles, steamed bread and liquor with methanol addition was less than 6.74%, and the recovery was 89.45-103.2% [65]. Xu et al. also determined melamine in milk by preparing dendritic AgNPs/AgNWs with the limit of detection of 10^{-10} mol·L^{-1} [66]. Moreover, Xu et al. have prepared centimeter-scale AuNPs/AgNWs composite materials with high nanometer-level roughness. The limiting concentration of Rhodamine B for this SERS substrate is 10^{-15} mol·L^{-1} [67]. Researchers also synthesized Fe_3O_4@Au core-shell nanomaterials, which can be used to detect acid orange II and brilliant blue in food samples [68].

5.4 Biotoxin detection

Natural toxins are a general term for a large class of biologically active substances, including animal toxins, phytotoxins, and microbial toxins. Different from synthetic toxic compounds, they can also be divided into marine toxins and agricultural toxins. Huang et al. reported a dual amplification strategy for the ultra-sensitive detection of biotoxins with the detection limit of 0.83 fg·mL^{-1}. This method was based on the specific target recognition of DNA aptamers, and the developed satellite core components generate many "hot spots" that can effectively enhance SERS signals [69]. Using the electrostatic interaction between halide ion, target, and Ag NPs, Tian et al. found that the coadsorption with the specific adsorbed I^- during the formation of hotspots could significantly improve the detection sensitivity. With the example of

the trace analysis of three tropane alkaloids (TAs) including scopolamine hydrobromide (SH), methscopolamine bromide (MB), and scopolamine butylbromide (SB), it was performed at a minimum detection concentration of 1 g·L^{-1} for these three substances under optimized conditions [70]. In addition, Sun et al. developed Fe_3O_4/SiO_2/Au/magnetic nanoparticles conjugated with tetrodotoxin (TTX) antibodies (Ab) and used as a Raman active substrate (Fe_3O_4/SiO_2/Au-Ab), the concentration of TTX with a limit of detection of 0.01 μg·mL^{-1} and a detection linearity range of 0.01-0.5 μg·mL^{-1} [71].

In another study, Müller et al. used amino-functionalized Ag nanoparticles as SERS probes to detect domoic acid (DA) biotoxins causing amnesic shellfish poisoning (ASP) in seawater with a detection limit of 0.033 ppb [72]. Besides, Han et al. proposed an exonuclease-assisted SERS sensing strategy and successfully constructed an aptamer-SERS for the determination of aflatoxin B_1 (AFB_1) in peanuts with a limit of detection (LOD) of 0.4 fg·mL^{-1} [73]. A novel SERS-based lateral flow (LF) assay has been reported by another researcher, which could detect *Yersinia pestis*, *Francisella tularensis*, and *Bacillus anthracis* with LODs at 43.4, 45.8, and 357 cfu·mL^{-1}, respectively [74]. Moreover, Han et al. combined the sensitivity of SERS technology to prepare a new type of MIP-SERS substrate for the detection of patulin. The linear range of the method was 5×10^{-10}-10^{-6} M with a limit of detection of 8.5×10^{-11} M [75].

5.5 Pesticide residues detection

In order to protect the health of consumers, many studies have reported the application of SERS for pesticide residues detection. For example, Chen et al. synthesized hollow Au@Ag-nanoflower-SERS sensor for competitive detection of 2,4-dichlorophenoxyacetic acid (2,4-D), and they developed antibody-functionalized magnetite nanoparticles (antibody-MNPs) as enrichment probe. The LOD was 0.11 ng·mL^{-1}, and its linear range was 0.001-100 ng·mL^{-1} with recoveries of 89.73-100.27% and RSDs of 2.56-4.97% [76]. In addition, Ekgasit et al. designed a simple and effective "paste-and-read" SERS method and prepared a biodegradable plasma silver nanoparticle-bacterial nanocellulose paper (AgNP-BNCP). A 3D SERS hot spot was formed on the substrate to directly detect 4-aminothiophenol and methomyl pesticides on oranges and apples, and the detection limit for methomyl was 3.6×10^{-7} M [77].

In another study, Lu et al. designed a novel MISPE-SERS chemosensor by combining molecularly imprinted polymers (MIPs) with SERS to detect thiabendazole in orange juice, the LOD was 4 ppm [78]. Moreover, researchers assembled a transparent AgNPs/PDMS composites on flexible PDMS surfaces, and measured crystal violet (CV) and thiram concentrations as low as 1×10^{-7} and 1×10^{-5} M in contaminated fish skin and orange peel, respectively [79]. In addition, Han et al. designed a gecko- inspired nanotentacle SERS (G-SERS) substrate to detect TMTD, MPT and MG in cucumbers, grapes, and apples. The LOD were 0.0012, 0.02, and 0.0003 mg·kg^{-1}, respectively [80]. Also, Hong et al. developed a highly homogeneous plasmonic SERS substrate by immobilizing gold nanoparticles on ultrafiltration (UF) membranes using a suction technique. The LOD of thiabendazole standard solution and thiabendazole in orange extract were 0.01 μg·mL^{-1} and 0.125 μg·g^{-1} [81]. In another study, a cellulose nanofiber (CNF) composite material coated with silver nanoparticles (AgNPs) was also developed to detect thiabendazole (TBZ) in apples with a detection limit of 5 ppm [82].

5.6 Residues of veterinary drug detection

Veterinary drug residues have become the most common contamination problem. The development of SERS-based technology is particularly important for the detection of veterinary drug residues. For example, Sun et al. developed a surface-enhanced Raman spectrometer based on thioglycolic acid (TGA)-functionalized silver-coated gold nanoparticles (Au@Ag-TGANPs) for rapid screening of thiamethoxam (TBZ) and ferbam in liquid milk with detection limits of 0.12 and 0.003 ppm [83]. Moreover, Zhao et al. developed a novel type of SERS of marbofloxacin established by using the interaction between marbofloxacin and β-cyclodextrin-silver nanoparticles. The method was used to determine the content of Marbofloxacin in chicken and duck mea t[84]. Huang et al. also developed an Ag/nanocellulose fibers for in-situ detection of foodstuffs, used rhodamine 6G as a probe to rapidly and accurately detect harmful residues on fish-fosfomycin, thiabendazole, malachite green, and enrofloxacin with the detection limits of 0.05, 0.09, 0.0014, and 0.069 ppm, respectively [85].

In addition, Wang et al. proposed a novel ultrasensitive SERS immunosensor based on the flower-shaped gold nanoparticles and magnetic beads to detect amantadine in chicken meat with a detection limit of 0.005 ng·mL^{-1} [86]. Also, Huang et al. fabricated uniform SiO_2@Au nanoparticles with excellent SERS activity, which can detect fipronil in 0.1 ppm [87]. In addition, another study used anti-kanamycin functionalized hybrid magnetic (Fe_3O_4)

nanoparticles (MNPs) and 2-mercaptobenzothiazole-labeled Au core@Ag shell nanoparticles as substrates. This sandwich assay measured the limit of detection (LOD) of kanamycin in milk to be 2 $pg \cdot mL^{-1}$ [88]. Moreover, Deng et al. prepared a SERS substrate using glass fiber paper to detect malachite green residues in fish. The detection limit was 5×10^{-10} $mol \cdot L^{-1}$ [89].

6 Future trends and perspectives

As a kind of quick and sensitive detection technology, SERS played a very important role in detecting heavy metal pollution, agricultural, and veterinary drug residue, misuse of food additives, foodborne pathogenic micro-organisms and so on. However, the SERS technology is still in its initial stage in the practical application of food safety detection, and it also faces corresponding challenges in theoretical analysis and quantitative analysis. First, SERS mechanism has not yet reached a clear point, and some SERS phenomena cannot be fully explained. Electromagnetic field enhancement mechanism and chemical enhancement mechanism are two main theoretical supports at present, but they have not been unanimously agreed. Therefore, the theoretical research on SERS still needs to be carried out continuously. Second, although there were various kinds of SERS substrate, problems such as instability, poor reproducibility, high cost and uneven structure were still faced. Complex two-dimensional or three-dimensional nanostructures can generate many "hot spots", but they are rarely used in food safety analysis, so further research in this area is not possible. Thirdly, since the signal strength of the same sample to be tested will be different under different test conditions, it is still a challenge to apply SERS to quantitative analysis. The quantitative accuracy still needs to be further studied. Fourth, the rapid determination of different samples requires the establishment of a unified Raman spectrum library. However, since the strength of SERS signal was affected by detection environment, the establishment of this gallery still needed to be done.

SERS technique showed great potential in the field of food safety. In the future, SERS technology can be combined with other techniques to improve the sensitivity, such as chemical separation technology, biological capture technology, etc. In order to obtain the results quickly and conveniently, the portable Raman spectrometer can be developed which has a broad prospect in the field of rapid detection.

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References

[1] Li D, Yao D, Li C, Luo Y, Liang A, Wen G, et al. Nanosol SERS quantitative analytical method: A review. TrAC-Trend Anal Chem. 2020; https://doi.org/127.10.1016/j.trac.2020.115885.

[2] Jiang GH, Wang ZY, Zong SF, Yang K, Zhu K, et al. Peroxidase-like recyclable SERS probe for the detection and elimination of cationic dyes in pond water. J Hazard Mater. 2020:124426. https://doi.org/10.1016/j.jhazmat.2020.124426.

[3] López-López M, García-Ruiz C. Infrared and Raman spectroscopy techniques applied to identification of explosives. TrAC-Trend Anal Chem. 2014;54:36-44. https://doi.org/10.1016/j.trac.2013.10.011.

[4] Joseph MM, Narayanan N, Nair JB, Karunakaran V, Ramya AN, Sujai PT, et al. Exploring the margins of SERS in practical domain: An emerging diagnostic modality for modern biomedical applications. Biomater. 2018;181:140-81. https://doi.org/10.1016/j.biomaterials.2018.07.045.

[5] Shen Z, Fan Q, Yu Q, Wang R, Wang H, Kong X. Facile detection of carbendazim in food using TLC-SERS on diatomite thin layer chromatography. Spectrochim Acta, Part A: Mol Biomol Spectrosc. 2021;247:119037. https://doi.org/10.1016/j.saa.2020.119037.

[6] Pang S, Yang T, He L. Review of surface enhanced Raman spectroscopic (SERS) detection of synthetic chemical pesticides. TrAC-Trend Anal Chem. 2016;85:73-82. https://doi.org/10.1016/j.trac.2016.06.017.

[7] Huang D, Zhao J, Wang M, Zhu S. Snowflake-like gold nanoparticles as SERS substrates for the sensitive detection of organophosphorus pesticide residues. Food Control. 2020;108:106835. https://doi.org/10.1016/j.foodcont.2019.106835.

[8] Ilhan H, Guven B, Dogan U, Torul H, Evran S, Çetin D, et al. The coupling of immunomagnetic enrichment of bacteria with paper-based platform. Talanta. 2019;201:245-52. https://doi.org/10.1016/j.talanta.2019.04.017.
[9] Blackie EJ, Le Ru EC, Etchegoin PG. Single-Molecule Surface-Enhanced Raman Spectroscopy of Nonresonant Molecules. J Am Chem Soc. 2009;131(40):14466-72. https://doi.org/10.1021/ja905319w.
[10] Lu X, Al-Qadiri HM, Lin M, Rasco BA. Application of Mid-infrared and Raman Spectroscopy to the Study of Bacteria. Food Biopro Technol. 2011;4(6):919-35. https://doi.org/10.1007/s11947-011-0516-8.
[11] Huang C-C, Cheng C-Y, Lai Y-S. Paper-based flexible surface enhanced Raman scattering platforms and their applications to food safety. Trends Food Sci Tech 2020;100:349-58. https://doi.org/10.1016/j.tifs.2020.04.019.
[12] Neng J, Zhang Q, Sun P. Application of surface-enhanced Raman spectroscopy in fast detection of toxic and harmful substances in food. Biosens Bioelectron. 2020;167. https://doi.org/10.1016/j.bios.2020.112480.
[13] Tong Q, Wang W, Fan Y, Dong L. Recent progressive preparations and applications of silver-based SERS substrates. TrAC-Trend Anal Chem. 2018;106:246-58. https://doi.org/10.1016/j.trac.2018.06.018.
[14] Liu Gk, Zheng H, Lu Jl. Recent progress and perspective of trace antibiotics detection in aquatic environment by surface-enhanced Raman spectroscopy. Trends Environ Anal. 2017;16:16-23. https://doi.org/10.1016/j.teac.2017.10.002.
[15] Mosier-Boss PA. Review of SERS Substrates for Chemical Sensing. Nanommaterials-Basel. 2017;7(6):142. https://doi.org/10.3390/nano7060142.
[16] Kearns H, Goodacre R, Jamieson LE, Graham D, Faulds K. SERS Detection of Multiple Antimicrobial-Resistant Pathogens Using Nanosensors. Anal Chem. 2017;89(23):12666-73. https://doi.org/10.1021/acs.analchem.7b02653.
[17] Li C, Ouyang H, Tang X, Wen G, Liang A, Jiang Z. A surface enhanced Raman scattering quantitative analytical platform for detection of trace Cu coupled the catalytic reaction and gold nanoparticle aggregation with label-free Victoria blue B molecular probe. Biosens Bioelectron. 2017;87:888-93. https://doi.org/10.1016/j.bios.2016.09.053.
[18] Yaseen T, Pu H, Sun D-W. Functionalization techniques for improving SERS substrates and their applications in food safety evaluation: A review of recent research trends. Trends Food Sci Tech. 2018;72:162-74. https://doi.org/10.1016/j.tifs.2017.12.012.
[19] Xu H, Aizpurua J, Käll M, Apell P. Electromagnetic contributions to single-molecule sensitivity in surface-enhanced Raman scattering. Phys. Rev. E. 2000;62(3):4318-24. https://doi.org/10.1103/PhysRevE.62.4318.
[20] Willets KA, Duyne RPV. Localized Surface Plasmon Resonance Spectroscopy and Sensing. Annu Rev Phys Chem. 2007;58(1):267-97. https://doi.org/10.1146/annurev.physchem.58.032806.104607.
[21] Fu X, Wang Y, Liu Y, Liu H, Fu L, Wen J, et al. A graphene oxide/gold nanoparticle-based amplification method for SERS immunoassay of cardiac troponin I. Analyst. 2019;144(5):1582-9. https://doi.org/10.1039/C8AN02022A.
[22] Ekmen E, Bilici M, Turan E, Tamer U, Zengin A. Surface molecularly-imprinted magnetic nanoparticles coupled with SERS sensing platform for selective detection of malachite green. Sensor Actuat B-Chem. 2020;325:128787. https://doi.org/10.1016/j.snb.2020.128787.
[23] Wang X, Zhu C, Hu X, Xu Q, Zhao H, Meng G, et al. Highly sensitive surface-enhanced Raman scattering detection of organic pesticides based on Ag-nanoplate decorated graphene-sheets. Appl Surf Sci. 2019;486:405-10. https://doi.org/10.1016/j.apsusc.2019.05.008.
[24] Guselnikova O, Postnikov P, Elashnikov R, Miliutina E, Svorcik V, Lyutakov O. Metal-organic framework (MOF-5) coated SERS active gold gratings: A platform for the selective detection of organic contaminants in soil. Anal Chim Acta. 2019;1068:70-9. https://doi.org/10.1016/j.aca.2019.03.058.
[25] Waiwijit U, Chananonnawathorn C, Eimchai P, Bora T, Hornyak GL, Nuntawong N. Fabrication of Au-Ag nanorod SERS substrates by co-sputtering technique and dealloying with selective chemical etching. Appl Surf Sci. 2020;530:147171. https://doi.org/10.1016/j.apsusc.2020.147171.
[26] Wang Q, Xu Z, Zhao Y, Zhangsun H, Bu T, Zhang C, et al. Bio-inspired self-cleaning carbon cloth based on flower-like Ag nanoparticles and leaf-like MOF: A high-performance and reusable substrate for SERS detection of azo dyes in soft drinks. Sensor Actuat B-Chem. 2020:129080. https://doi.org/10.1016/j.snb.2020.129080.
[27] Chamuah N, Bhuyan N, Das PP, Ojah N, Choudhary AJ, Medhi T, et al. Gold-coated electrospun PVA nanofibers as SERS substrate for detection of pesticides. Sensor Actuat B-Chem. 2018;273:710-7. https://doi.org/10.1016/j.snb.2018.06.079.
[28] Bastús NG, Comenge J, Puntes V. Kinetically Controlled Seeded Growth Synthesis of Citrate-Stabilized Gold Nanoparticles of up to 200 nm: Size Focusing versus Ostwald Ripening. Langmuir. 2011;27(17):11098-105. https://doi.org/10.1021/la201938u.
[29] Bastús NG, Merkoçi F, Piella J, Puntes V. Synthesis of Highly Monodisperse Citrate-Stabilized Silver Nanoparticles of up to 200 nm: Kinetic Control and Catalytic Properties. Chem Mater. 2014;26(9):2836-46. https://doi.org/10.1021/cm500316k.
[30] D'Elia V, Rubio-Retama J, Ortega-Ojeda FE, García-Ruiz C, Montalvo G. Gold nanorods as SERS substrate for the ultratrace detection of cocaine in non-pretreated oral fluid samples. Colloid Surface A. 2018;557:43-50. https://doi.org/10.1016/j.colsurfa.2018.05.068.
[31] Wang H, Li KB, Xu C, Xu SC, Li GH. Large-scale solvothermal synthesis of Ag nanocubes with high SERS activity. J Alloy Compd. 2019;772:150-6. https://doi.org/10.1016/j.jallcom.2018.09.043.
[32] Pu H, Huang Z, Xu F, Sun D-W. Two-dimensional self-assembled Au-Ag core-shell nanorods nanoarray for sensitive detection of thiram in apple using surface-enhanced Raman spectroscopy. Food Chem. 2021;343:128548. https://doi.org/10.1016/j.foodchem.2020.128548.
[33] He XY, Ge C, Zheng XQ, Tang B, Chen L, Li SB, et al. Rapid identification of alpha-fetoprotein in serum by a microfluidic SERS chip integrated with Ag/Au Nanocomposites. Trends Food Sci Tech. 2018; https://doi.org/10.1016/j.tifs.2018.02.020.

[34] Toderas F, Baia M, Baia L, Astilean S. Controlling gold nanoparticle assemblies for efficient surface-enhanced Raman scattering and localized surface plasmon resonance sensors. Nanotechnology. 2007;18(25):255702. https://doi.org/10.1088/0957-4484/18/25/255702.

[35] Zhang L. Self-assembly Ag nanoparticle monolayer film as SERS Substrate for pesticide detection. Appl Surf Sci. 2013;270:292-4. https://doi.org/10.1016/j.apsusc.2013.01.014.

[36] Sivashanmugan, K., Nguyen, V.-H. & Nguyen, B.-S. Tailoring a novel Au nanodot arrays on graphene substrate for a highly active Surface-Enhanced Raman Scattering (SERS). Mater Lett. 2020;271:127807. https://doi.org/10.1016/j.matlet.2020.127807.

[37] Liu, B. et al. Detection of Pesticides in Fruits by Surface-Enhanced Raman Spectroscopy Coupled with Gold Nanostructures. Food Bioprocess Tech. 2012;6: 710-718, https://doi.org/10.1007/s11947-011-0774-5.

[38] Cottat M, Lidgi-Guigui N, Tijunelyte I, Barbillon G, Hamouda F, Gogol P, et al. Soft UV nanoimprint lithography-designed highly sensitive substrates for SERS detection. Anoscale Res Lett. 2014;9(1):623. https://doi.org/10.1186/1556-276X-9-623.

[39] Wu H, Luo Y, Hou C, Huo D, Zhou Y, Zou S, et al. Flexible bipyramid-AuNPs based SERS tape sensing strategy for detecting methyl parathion on vegetable and fruit surface. Sensor Actuat B-Chem. 2019;285:123-8. https://doi.org/10.1016/j.snb.2019.01.038.

[40] Han XX, Ozaki Y, Zhao B. Label-free detection in biological applications of surface-enhanced Raman scattering. TrAC-Trend Anal Chem. 2012;38:67-78. https://doi.org/10.1016/j.trac.2012.05.006.

[41] Liu Y, Zhou H, Hu Z, Yu G, Yang D, Zhao J. Label and label-free based surface-enhanced Raman scattering for pathogen bacteria detection: A review. Biosens Bioelectron. 2017;94:131-40. https://doi.org/10.1016/j.bios.2017.02.032.

[42] Hernández Y, Lagos LK, Galarreta BC. Development of a label-free-SERS gold nanoaptasensor for the accessible determination of ochratoxin A. Sens Bio-Sens Res. 2020;28:100331. https://doi.org/10.1016/j.sbsr.2020.100331.

[43] Du Y, Liu H, Chen Y, Tian Y, Zhang X, Gu C, et al. Recyclable label-free SERS-based immunoassay of PSA in human serum mediated by enhanced photocatalysis arising from Ag nanoparticles and external magnetic field. Appl Surf Sci. 2020;528:146953. https://doi.org/10.1016/j.apsusc.2020.146953.

[44] Zheng X-S, Jahn IJ, Weber K, Cialla-May D, Popp J. Label-free SERS in biological and biomedical applications: Recent progress, current challenges and opportunities. Spectrochim Acta, Part A: Mol Biomol Spectrosc. 2018;197:56-77. https://doi.org/10.1016/j.saa.2018.01.063.

[45] Li H, Arroyo-Currás N, Kang D, Ricci F, Plaxco KW. Dual-Reporter Drift Correction To Enhance the Performance of Electrochemical Aptamer-Based Sensors in Whole Blood. J Am Chem Soc. 2016;138(49):15809-12. https://doi.org/10.1021/jacs.6b08671.

[46] Lu D, Lin X, Chen C, Lu Y, Feng S, Huang Z, et al. Interference-free SERS tags for ultrasensitive quantitative detection of tyrosinase in human serum based on magnetic bead separation. Anal Chim Acta. 2020;1138:150-7. https://doi.org/10.1016/j.aca.2020.09.042.

[47] Zhang W, Tang S, Jin Y, Yang C, He L, Wang J, et al. Multiplex SERS-based lateral flow immunosensor for the detection of major mycotoxins in maize utilizing dual Raman labels and triple test lines. J Hazard Mater. 2020;393:122348. https://doi.org/10.1016/j.jhazmat.2020.122348.

[48] Song C, Li J, Sun Y, Jiang X, Zhang J, Dong C, et al. Colorimetric/SERS dual-mode detection of mercury ion via SERS-Active peroxidase-like Au@AgPt NPs. Sensor Actuat B-Chem. 2020;310:127849. https://doi.org/10.1016/j.snb.2020.127849.

[49] Wu Y, Fu C, Xiang J, Cao Y, Deng Y, Xu R, et al. "Signal-on" SERS sensing platform for highly sensitive and selective Pb2+ detection based on catalytic hairpin assembly. Anal Chim Acta. 2020;1127:106-13. https://doi.org/10.1016/j.aca.2020.06.038.

[50] Zhou L, Yang J, Wang X, Song G, Lu F, You L, et al. Ag nanoparticles decorated Ag@ZrO2 composite nanospheres as highly active SERS substrates for quantitative detection of hexavalent chromium in waste water. J Mol Liq. 2020;319:114158. https://doi.org/10.1016/j.molliq.2020.114158.

[51] Halkare P, Punjabi N, Wangchuk J, Nair A, Kondabagil K, Mukherji S. Bacteria functionalized gold nanoparticle matrix based fiber-optic sensor for monitoring heavy metal pollution in water. Sensor Actuat B-Chem. 2019;281:643-51. https://doi.org/10.1016/j.snb.2018.10.119.

[52] Zhao Y, Yamaguchi Y, Ni Y, Li M, Dou X. A SERS-based capillary sensor for the detection of mercury ions in environmental water. Spectroc Acta Pt A-Molec Biomolec Spectr. 2020;233:118193. https://doi.org/10.1016/j.saa.2020.118193.

[53] Franciscato DS, Matias TA, Shinohara J, Gonçalves JM, Coelho NP, Fernandes CS, et al. Thiosemicarbazone@Gold nanoparticle hybrid as selective SERS substrate for Hg2+ ions. Spectroc Acta Pt A-Molec Biomolec Spectr. 2018;204:174-9. https://doi.org/10.1016/j.saa.2018.06.038.

[54] Song L, Mao K, Zhou X, Hu J. A novel biosensor based on Au@Ag core–shell nanoparticles for SERS detection of arsenic (III). Talanta. 2016;146:285-90. https://doi.org/10.1016/j.talanta.2015.08.052.

[55] Liu S, Li H, Hassan MM, Ali S, Chen Q. SERS based artificial peroxidase enzyme regulated multiple signal amplified system for quantitative detection of foodborne pathogens. Food Control. 2020:107733. https://doi.org/10.1016/j.foodcont.2020.107733.

[56] Chattopadhyay S, Sabharwal PK, Jain S, Kaur A, Singh H. Functionalized polymeric magnetic nanoparticle assisted SERS immunosensor for the sensitive detection of S. typhimurium. Anal Chim Acta. 2019;1067:98-106. https://doi.org/10.1016/j.aca.2019.03.050.

[57] Wu S, Duan N, He C, Yu Q, Dai S, Wang Z. Surface-enhanced Raman spectroscopic–based aptasensor for Shigella sonnei using a dual-functional metal complex-ligated gold nanoparticles dimer. Colloid Surf B-Biointerfaces. 2020;190:110940. https://doi.org/10.1016/j.colsurfb.2020.110940.

[58] Zhao M, Yao X, Liu S, Zhang H, Wang L, Yin X, et al. Antibiotic and mammal IgG based lateral flow assay for simple and sensitive detection of Staphylococcus aureus. Food Chem. 2021;339:127955. https://doi.org/10.1016/j.foodchem.2020.127955.

[59] Zhu A, Ali S, Xu Y, Ouyang Q, Chen Q. A SERS aptasensor based on AuNPs functionalized PDMS film for selective and sensitive detection of Staphylococcus aureus. Biosens Bioelectron. 2021;172:112806. https://doi.org/10.1016/j.bios.2020.112806.

[60] Huang D, Zhuang Z, Wang Z, Li S, Zhong H, Liu Z, et al. Black phosphorus-Au filter paper-based three-dimensional SERS substrate for rapid detection of foodborne bacteria. Appl Surf Sci. 2019;497:143825. https://doi.org/10.1016/j.apsusc.2019.143825.

[61] Díaz-Amaya S, Lin L-K, Deering AJ, Stanciu LA. Aptamer-based SERS biosensor for whole cell analytical detection of E. coli O157:H7. Anal Chim Acta. 2019;1081:146-56. https://doi.org/10.1016/j.aca.2019.07.028.

[62] Pang Y, Wan N, Shi L, Wang C, Sun Z, Xiao R, et al. Dual-recognition surface-enhanced Raman scattering(SERS) biosensor for pathogenic bacteria detection by using vancomycin-SERS tags and aptamer-Fe3O4@Au. Anal Chim Acta. 2019;1077:288-96. https://doi.org/10.1016/j.aca.2019.05.059.

[63] Tang W, An Y, Ho Row K. Fabrication of Au nanoparticles embedded holey g-C3N4 as SERS substrates for sensitive and reliable detection. Chem Eng J. 2020;402:126194. https://doi.org/10.1016/j.cej.2020.126194.

[64] Duan N, Qi S, Guo Y, Xu W, Wu S, Wang Z. Fe3O4@Au@Ag nanoparticles as surface-enhanced Raman spectroscopy substrates for sensitive detection of clenbuterol hydrochloride in pork with the use of aptamer binding. LWT. 2020;134:110017. https://doi.org/10.1016/j.lwt.2020.110017.

[65] Zhao YX, Zhu WW, Wu YY, Chen YY, Du FK, Yan J, et al. Sensitive surface-enhanced Raman scattering for the quantitative detection of formaldehyde in foods using gold nanorod substrate. Microchem J. 2021;160:105727. https://doi.org/10.1016/j.microc.2020.105727.

[66] Xu D, Jiang H, Zhang S, Yang W, Guo Q, Zhang Y, et al. Centimeter-scale high nanoscale roughness silver nanoparticles decorated silver nanowires: A highly sensitive material towards melamine in milk. Opt Mater. 2020;109:110471. https://doi.org/10.1016/j.optmat.2020.110471.

[67] Xu D, Jiang H, Zhang S, Yang W, Zhang Y, Wang Z, et al. High roughness gold nanoparticles/silver nanowires composites: Fabrication, characterization and ultrasensitive SERS detection towards Rhodamine B. Microchem J. 2020;158:105136. https://doi.org/10.1016/j.microc.2020.105136.

[68] Xie Y, Chen T, Guo Y, Cheng Y, Qian H, Yao W. Rapid SERS detection of acid orange II and brilliant blue in food by using Fe3O4@Au core–shell substrate. Food Chem. 2019;270:173-80. https://doi.org/10.1016/j.foodchem.2018.07.065.

[69] Huang D, Chen J, Ding L, Guo L, Kannan P, Luo F, et al. Core-satellite assemblies and exonuclease assisted double amplification strategy for ultrasensitive SERS detection of biotoxin. Anal Chim Acta. 2020;1110:56-63. https://doi.org/10.1016/j.aca.2020.02.058.

[70] Lu J, Cai Z, Zou Y, Wu D, Wang A, Chang J, et al. Silver Nanoparticle-Based Surface-Enhanced Raman Spectroscopy for the Rapid and Selective Detection of Trace Tropane Alkaloids in Food. ACS Applied Nano Materials. 2019;2(10):6592-601. https://doi.org/10.1021/acsanm.9b01493.

[71] Neng J, Wang X, Jia K, Sun P. Rapid Detection of Tetrodotoxin Using Surface-Enhanced Raman Spectroscopy and Fe3O4/SiO2/Au Gold/Magnetic Nanoparticles. J Appl Spectrosc. 2018;85(1):160-5. https://doi.org/10.1007/s10812-018-0627-3.

[72] Müller C, Glamuzina B, Pozniak I, Weber K, Cialla D, Popp J, et al. Amnesic shellfish poisoning biotoxin detection in seawater using pure or amino-functionalized Ag nanoparticles and SERS. Talanta. 2014;130:108-15. https://doi.org/10.1016/j.talanta.2014.06.059.

[73] Li Q, Lu Z, Tan X, Xiao X, Wang P, Wu L, et al. Ultrasensitive detection of aflatoxin B1 by SERS aptasensor based on exonuclease-assisted recycling amplification. Biosens Bioelectron. 2017;97:59-64. https://doi.org/10.1016/j.bios.2017.05.031.

[74] Wang R, Kim K, Choi N, Wang X, Lee J, Jeon JH, et al. Highly sensitive detection of high-risk bacterial pathogens using SERS-based lateral flow assay strips. Sensor Actuat B-Chem. 2018;270:72-9. https://doi.org/10.1016/j.snb.2018.04.162.

[75] Zhu Y, Wu L, Yan H, Lu Z, Yin W, Han H. Enzyme induced molecularly imprinted polymer on SERS substrate for ultrasensitive detection of patulin. Anal Chim Acta. 2020;1101:111-9. https://doi.org/10.1016/j.aca.2019.12.030.

[76] Xu Y, Kutsanedzie FYH, Hassan MM, Zhu J, Li H, Chen Q. Functionalized hollow Au@Ag nanoflower SERS matrix for pesticide sensing in food. Sensor Actuat B-Chem. 2020;324:128718. https://doi.org/10.1016/j.snb.2020.128718.

[77] Parnsubsakul A, Ngoensawat U, Wutikhun T, Sukmanee T, Sapcharoenkun C, Pienpinijtham P, et al. Silver nanoparticle/bacterial nanocellulose paper composites for paste-and-read SERS detection of pesticides on fruit surfaces. Carbohydr Polym. 2020;235:115956. https://doi.org/10.1016/j.carbpol.2020.115956.

[78] Feng J, Hu Y, Grant E, Lu X. Determination of thiabendazole in orange juice using an MISPE-SERS chemosensor. Food Chem. 2018;239:816-22. https://doi.org/10.1016/j.foodchem.2017.07.014.

[79] Alyami A, Quinn AJ, Iacopino D. Flexible and transparent Surface Enhanced Raman Scattering (SERS)-Active Ag NPs/PDMS composites for in-situ detection of food contaminants. Talanta. 2019;201:58-64. https://doi.org/10.1016/j.talanta.2019.03.115.

[80] Wang P, Wu L, Lu Z, Li Q, Yin W, Ding F, et al. Gecko-Inspired Nanotentacle Surface-Enhanced Raman Spectroscopy Substrate for Sampling and Reliable Detection of Pesticide Residues in Fruits and Vegetables. Anal Chem. 2017;89(4):2424-31. https://doi.org/10.1021/acs.analchem.6b04324.

[81] Hong J, Kawashima A, Hamada N. A simple fabrication of plasmonic surface-enhanced Raman scattering (SERS) substrate for pesticide analysis via the immobilization of gold nanoparticles on UF membrane. Appl Surf Sci. 2017;407:440-6. https://doi.org/10.1016/j.apsusc.2017.02.232.

[82] Liou P, Nayigiziki FX, Kong F, Mustapha A, Lin M. Cellulose nanofibers coated with silver nanoparticles as a SERS platform for detection of pesticides in apples. Carbohydr Polym. 2017;157:643-50. https://doi.org/10.1016/j.carbpol.2016.10.031.

[83] Hussain A, Pu H, Hu B, Sun DW. Au@Ag-TGANPs based SERS for facile screening of thiabendazole and ferbam in liquid milk. Spectrochim. Acta, Part A. 2021;245:118908. https://doi.org/10.1016/j.saa.2020.118908.
[84] Zhao R, Bi S, Shao D, Sun X, Li X. Rapid determination of marbofloxacin by surface-enhanced Raman spectroscopy of silver nanoparticles modified by β-cyclodextrin. Spectrochim. Acta, Part A. 2020;229:118009. https://doi.org/10.1016/j.saa.2019.118009.
[85] Chen J, Huang M, Kong L. Flexible Ag/nanocellulose fibers SERS substrate and its applications for in-situ hazardous residues detection on food. Appl Surf Sci. 2020;533:147454. https://doi.org/10.1016/j.apsusc.2020.147454.
[86] Ma M, Sun J, Chen Y, Wen K, Wang Z, Shen J, et al. Highly sensitive SERS immunosensor for the detection of amantadine in chicken based on flower-like gold nanoparticles and magnetic bead separation. Food Chem Toxicol. 2018;118:589-94. https://doi.org/10.1016/j.fct.2018.06.013.
[87] Muhammad M, Yao G, Zhong J, Chao K, Aziz MH, Huang Q. A facile and label-free SERS approach for inspection of fipronil in chicken eggs using SiO2@Au core/shell nanoparticles. Talanta. 2020;207:120324. https://doi.org/10.1016/j.talanta.2019.120324.
[88] Zengin A, Tamer U, Caykara T. Extremely sensitive sandwich assay of kanamycin using surface-enhanced Raman scattering of 2-mercaptobenzothiazole labeled gold@silver nanoparticles. Anal Chim Acta. 2014;817:33-41. https://doi.org/10.1016/j.aca.2014.01.042.
[89] Deng D, Lin Q, Li H, Huang Z, Kuang Y, Chen H, et al. Rapid detection of malachite green residues in fish using a surface-enhanced Raman scattering-active glass fiber paper prepared by in situ reduction method. Talanta. 2019;200:272-8. https://doi.org/10.1016/j.talanta.2019.03.021.