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REVIEW

Applications of surface-enhanced Raman spectroscopy based on portable Raman spectrometers: A review of recent developments

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Abstract

Recently, the surface-enhanced Raman spectroscopy (SERS) technique emerges as a potential promising analytical tool for rapid, sensitive, and selective detection which can provide unique information about the substances in the presence of plasmonic nanostructures via finger-printing SERS spectra. The progress in nanostructure SERS substrates and portable Raman spectrometers will promote this novel detection technique to play an important role in the future rapid on-site assay. In this review, we summarized the latest research on SERS detection technique combined based on nanostructure SERS-active substrates with portable Raman spectrometers and their potential on-site detection applications in environment pollutants, agricultural pollutants, biomedical analysis, and other newly emerging fields (focusing particularly on the last 5 years of research). The future perspective of SERS for on-site analysis is also discussed.

KEYWORDS
application, on-site, portable Raman spectrometers, SERS, substrate

1 | INTRODUCTION

Since 1974, Fleischmann and coworkers obtained the first high-intensity Raman scattering signal of pyridine on the rough silver (Ag) electrode surface, which marked the beginning of surface-enhanced Raman spectroscopy (SERS).[1] In 1977, Jeanmaire and Van Duyne[2] and Albrecht and Creighton[3] further found that the Raman signal of pyridine on the rough Ag electrode surface was nearly six orders of magnitude higher than that in an untreated solution. Since then, other research groups have explored the phenomenon and confirmed that the phenomenon of Raman signal enhancement on the rough metal surface is due to the surface enhancement effect of the rough metal surface, and this phenomenon is called SERS.

The excitation of the surface plasmon will enhance the electromagnetic field on the surface of the analyte molecule, which makes the Raman signal of the analyte molecule much larger than the normal Raman signal. SERS can obtain more detailed molecular structure information that is difficult to obtain by ordinary Raman. The research on the enhancement mechanism of SERS is relatively complicated.[4] At present, the academic community generally agrees with the following two conjectures: electromagnetic enhancement mechanism (EM) and charge transfer enhancement mechanism (CM).[5–7] The EM is a physical enhancement model, when the surface plasmon is excited to a high energy level, the plasma oscillates. When the frequency of the electromagnetic wave and the oscillation frequency of the plasma are the same, the coupling resonance between the plasma and the photoelectric field occurs, and the local electric field on the metal surface will be sharply enhanced, which will amplify the electric field of the incident light and cause the Raman scattering to be enhanced.[8,9] The CM represents the interaction between the analytes and enhancement substrate, which can be classified as off-resonance chemical enhancement model, molecular resonance model or charge transfer model.[10,11] After a large number of experiments, the researchers found that the SERS effect cannot be reasonably explained by only one of two mechanisms.[12–14] The enhancement contributions of the two mechanisms to various systems are usually different.

With the development of miniaturized, intelligent, portable Raman spectrometers, SERS technique is widely used for rapid, on-site, real-time analysis. The advancement of some remarkable technology has led to the development of Raman spectrometers, such as the increasing miniaturization of laser sources or the advent of charge-coupled device (CCD). Therefore, portable and mobile instruments have been produced for detection outside the laboratory, especially on-site tests.

Through nearly 50 years of development, SERS has become a promising tool in various fields, including chemistry,[15–18] physics,[19–21] and biology.[22–24] The critical step and basic focus for the practical application of SERS technology is the construction of SERS substrates, because the practical application of SERS technology depends on the reproducibility and activity of the substrates.

2 | SERS SUBSTRATES

With the deepening understanding of nanostructures, the application of SERS has been continuously developed. In recent years, SERS substrates of different shapes, compositions, and sizes have been developed with the advancement of nanotechnology, lasers, electronics, and optics, which can generate various enhancement factors (EFs) and are widely used in trace analysis. Generally, SERS-active nanostructures can be divided into three types of substrates: nano-colloid substrates, rigid substrates and flexible substrates.

2.1 | Nano-colloid substrates

So far, spherical metal nano-colloids remain the most widely used SERS substrates.[25–27] The simplest and most common method to synthesize spherical metal nanoparticles is by reducing metal salt solutions, usually using different reducing and blocking agents. Common chemical reducing agents include sodium citrate,[28] sodium borohydride ($NaBH_4$),[29] hydroxylamine hydrochloride,[30] and hydrazine hydrate.[31] Metal nanoparticles with different morphologies, particle size distributions, and aggregation degrees can be synthesized by controlling the reaction temperature, pH value of the solution, types of metal salts, reducing agents and surfactants.

Gold (Au) and Ag nanoparticles are the most widely used as enhancement substrates in SERS research. Among these methods to synthesize gold nanoparticles (AuNPs), the sodium citrate reduction approach is the earliest discovered and the most widely used. As early as 1951, Turkevich et al reported that AuNPs could be reduced from Au trivalent compounds using sodium citrate.[32] In 1973, Frens prepared AuNPs with particle size distribution in the range 16–147 nm by changing the ratio between sodium citrate and Au solution.[33]

One of the most typical methods for preparing Ag sols for SERS substrates is the reduction of boiling silver nitrate ($AgNO_3$) solution using sodium citrate proposed by Lee and Meisel.[28] This method can obtain silver nanoparticles (AgNPs) with sizes ranging from 60 to 80 nm. The colloids show turbid gray-green and the maximum surface plasmon absorption is at 410 nm. Based on the method of Lee and Meisel, Leopold and Lendl used hydroxylamine hydrochloride as a reducing agent instead of sodium citrate to rapidly obtain Ag sol with high SERS activity at room temperature.[34]

In recent years, with the rapid development of nanosynthesis technology, not only spherical nanoparticles can be used as SERS substrates, but other metal nanoparticles with different morphologies have also been synthesized and used in SERS technique.[35–37] Surfactants are the most widely used in the synthesis of nanocolloids with special morphology. On the one hand, they can prevent the agglomeration of nanoparticles, and on the other hand, they can effectively control the formation of specific sizes and shapes of nanoparticles. Gold nanorods (AuNRs) are non-spherical nanoparticles with relatively simple morphology. In general, they are synthesized by a seed growth method, and chloroauric acid ($HAuCl_4$) is reduced by $NaBH_4$ to obtain Au seeds with a particle size of about 2 nm. Cetyltrimethylammonium bromide (CTAB) is used as a capping agent and ascorbic acid (AA) is used as a reducing agent.[38] Gold nanocubes (AuNCs) have eight vertices, which can provide more hot spots.[39,40] Gold nanostars (AuNSs) have more tips, and the seed growth method is usually used. In the mixed solution of acidic (hydrochloric acid) $HAuCl_4$ and Au seeds, $AgNO_3$ and AA are rapidly added at the same time.[41] Gold nanoflowers (AuNFs) have a rougher surface and more abundant hot spots. A simple synthesis method is to use pH 7.4 HEPES aqueous solution mixed with $HAuCl_4$ to stand at room temperature.[42]

Core-shell nanoparticles are also a kind of SERS substrate material that has been studied extensively in recent years.[43,44] The optical properties and electronic structures of core-shell nanoparticles can be altered due to the shell coated on the core compared to individual metal nanoparticles. The seed growth method is the most commonly method for the preparation of Au-Ag core-shell nanomaterials, that is, using the nanoparticle element formed by an element as the crystal nucleus, and using the method of chemical reduction, the elemental material of other metal elements is deposited on its surface to obtain Au and Ag core-shell structures. However, the control steps are more complex and not suitable for batch preparation.

Therefore, for the detection of an actual sample, the nano-colloidal SERS substrate has an obvious advantage that it can be mass-produced and divided into small portions after being combined. This not only guarantees batch-to-batch uniformity to a certain extent, but also reduces the production cost of the material, and is easy to store and transport. What is more, it is usually single-use and then thrown away, which eliminates issues such as cross-contamination between samples in use on solid substrates.

2.2 | Rigid SERS substrates

In addition, metal nanoparticles are assembled on quart,[45] glass,[6] silicon wafers[46] or other rigid materials as rigid SERS substrates. Traditional physical deposition techniques are used to immobilize precious metal nanomaterials on rigid substrates to prepare SERS substrates. In recent years, significant progress has also been made in the direct imprinting of nanostructured noble metals onto solid supports for SERS substrate preparation using relatively advanced techniques. Top-down nanofabrication techniques such as focused ion beam (FIB), electron beam lithography (EBL), and relatively advanced methods such as photolithography can determine the shape, size, and relative distance between plasmonic nanostructures and relative orientation for fine control.

However, rigid SERS substrates cannot directly carry out sample collection and non-destructive testing. Such substrates must undergo a series of pretreatments and then dropped onto the SERS substrates before detection. For instance, the general approach for conventional rigid substrate-based SERS detection requires the complicated extraction of analytes from objects of interest and tedious sample preparation steps before the adsorption of analytes on the SERS substrate for analyses, which is not suitable for practical applications. This process may take a lot of time. Besides, glass, silicon wafer, etc. are hard and brittle, lack flexibility and cannot be used for surface analysis, all of which limit the advantages of SERS technique such as rapid on-site detection.

2.3 | Flexible SERS substrates

Flexible SERS substrates are one of the most rapidly developing new substrates in recent years.[47–49] The flexible SERS substrate uses a deformable flexible carrier as the main body while continuing the high sensitivity of the traditional SERS substrate, which has dual functions of sampling and enhancing Raman signals. Compared with rigid SERS substrates, the flexible SERS substrates have certain deformability which makes it more universal and convenient when sampling and testing objects with irregular surfaces, and can easily achieve *in situ*, non-destructive, and rapid on-site testing.

According to the different flexible carriers, flexible SERS substrates can be divided into three types: (1) Flexible SERS substrates prepared by directly using existing commercial flexible materials as carriers; (2) flexible SERS substrates prepared by using high-molecular polymer as carriers; (3) flexible SERS substrates prepared using other functional materials as carriers.

Commercial flexible materials such as tape, paper, swab, sponge and other sheet materials have been widely used for flexible SERS substrates preparation.[50–52] The tape is sticky and can be directly extracted and detected by the 'stick-peel' method on the actual sample surfaces.

Flexible SERS substrates based on high-molecular weight polymers can flexibly adjust the physicochemical properties of the substrates, such as shape, viscoelasticity, fluidity, hydrophobicity, etc., according to different reaction conditions, so as to directionally synthesize functional flexible SERS substrates according to the purpose of use. Flexible SERS substrates prepared from polymers include two-dimensional (2D) membrane SERS substrates, three-dimensional (3D) porous SERS substrates, etc. The use of high-molecular polymers to prepare film-like SERS substrates by template method is one of the most studied types.

Fabrication of flexible SERS substrates using other functional materials such as capillary tube has also been reported. Since gold trioctahedron (AuTOH) has superior SERS characteristics, combined with capillary, it can realize the advantages of SERS signal amplification and trace analysis.[53] Such SERS substrates often have their own unique advantages in certain fields. However, their preparation methods often require support or high temperature and high pressure to complete the preparation, which is relatively more complicated than the first two types.

Despite the impressive advantages of the flexible SERS substrate, the complex preparation process and difficulty of recovery significantly increase the detection cost and limit its practical application for on-site testing. Researchers made great efforts on fabricating flexible SERS substrates which can be a positive force for the SERS application in real life.[54–56]

3 | SERS APPLICATIONS BASED ON PORTABLE RAMAN SPECTROMETERS

SERS is a promising tool for rapid, sensitive and selective detection and analysis. This is mainly due to its potential to simplify sample preprocessing, huge detectable signal amplification and fingerprint SERS spectra for rapid target analyte identification. With the advancement of technology, the miniaturization of Raman instruments is undoubtedly an ideal choice for promoting SERS to on-site applications. Owing to the gradual popularization of portable Raman spectrometers, SERS technology has achieved unprecedented development in on-site rapid detection in the fields such as food safety, environmental safety, and biomedical analysis.

3.1 | Environment pollutants

3.1.1 | Detection of ions

Toxic ions are the most common bioaccumulative pollutants which cause serious damage to human health and toxic ion pollution is a global problem. Among them, mercury ion (Hg^{2+}) is one of the most toxic ions, which can be evaporated into mercury vapor at room temperature. Trace amounts of mercury vapor can be highly toxic and seriously endanger public health.[57] Therefore, it is urgent to develop highly sensitive and accurate determination methods for Hg^{2+}. Unlike organic or biological molecules with large cross-section, Hg^{2+} shows only a small Raman signal. Therefore, Hg^{2+} could only be measured by indirect signal readout rather than direct signal readout. Based on this principle, Song and coworkers found that the SERS signal was sensitive to the presence of Hg^{2+} when methimazole was adsorbed on cyclodextrin-protected AgNPs. When the Hg^{2+} existed, methimazole molecules would be desorbed from the surface of AgNPs, resulting in a weakened SERS signal. The analytical range is from 0.50 μg/L to 150 μg/L with the limit of detection (LOD) of 0.10 μg/L.[58] Owing to rhodamine 6G (R6G) having a large cross-section strong Raman signals are exhibited, therefore Song and coworkers developed another probe based on R6G-bonded and amino group functionalized core-shell nanorods, such that the concentration of superlow Hg^{2+} (0.33 pM) could be detected with a portable Raman spectrometer.[59] Jiang and coworkers developed a SERS approach for the determination of Hg^{2+} in a real sample based on aptamer-regulating graphene (GO) nanocatalysis. The prepared GO could catalyze the reduction reaction between $HAuCl_4$ and trisodium citrate, further promote the generation of AuNPs. Owing to the continuous formation of AuNPs, the SERS intensity increased with the concentration of nanocatalyst GO. The SERS signal was linearly related to the Hg^{2+} concentration ranging from 0.25 to 10 nM with the LOD of 0.08 nM.[60]

To date, SERS detection for solid matrices or liquid substances is always performed horizontally. However, when detecting liquids in the field, the level of accuracy can be compromised, especially using portable Raman equipment for on-site analysis. Thus, researchers have developed many methods for detecting Hg^{2+} based on solid SERS substrates to solve this problem. Liao et al prepared Au@Ag core-shell nanoparticles embedded with 4-mercaptobenzoic acid (Au@4-MBA@Ag) as a SERS probe which was fixed on the inner wall of the glass capillary for the determination of Hg^{2+} with a portable Raman spectrometer. The LOD was as low as 0.03 nM (Figure 1a).[61] Similarly, Zhao et al prepared a SERS sensor to detect Hg^{2+} by decorating the capillary inner wall with 4,4′-dipyridyl functionalized silver nanoparticles (Dpy-AgNPs). The LOD was as low as 0.1 ppb.[62]

Given that the continuous expansion of industrialization, a large amount of hexavalent chromium (Cr(VI)) will be discharged into environmental water through industrial wastewater. However, Cr(VI) is extremely harmful to the public health which can lead to skin lesions, lung inflammation, and cancer of the respiratory tract, even death. Thus, it is urgent to establish fast and accurate on-site Cr(VI) detection methods. Tian and coworkers proposed a SERS method based on sodium alginate protected silver nanoparticles (SA-AgNPs) for the determination of Cr(VI) by a portable Raman spectroscopy within 10 s. Carbimazole was used as the SERS reporter to detect Cr(VI) in the water based on the redox reaction of carbimazole with Cr(VI) and the LOD was 1.01×10^{-9} M.[63] Shao and coworkers developed a quantitative analysis of Cr(VI) in aqueous solutions with SERS method. After the addition of Cr(VI)-containing samples to the AgNPs colloidal solution, aggregating salts were introduced to aggregate nanoparticles and enhance the SERS signals. The method exhibited high sensitivity with a LOD of 0.72 ppb.[64] In addition, SERS methods, for the analysis of other heavy metals in the environment using a portable Raman spectrometer, have also been developed, such as zinc ion (Zn^{2+}),[65] arsenic(III),[66] lead(II)[67] etc.

3.1.2 | Determination of dye

Fungicides and repellents, such as malachite green (MG), acid orange II (AO II), crystal violet (CV), R6G, and methylene blue (MB) have been

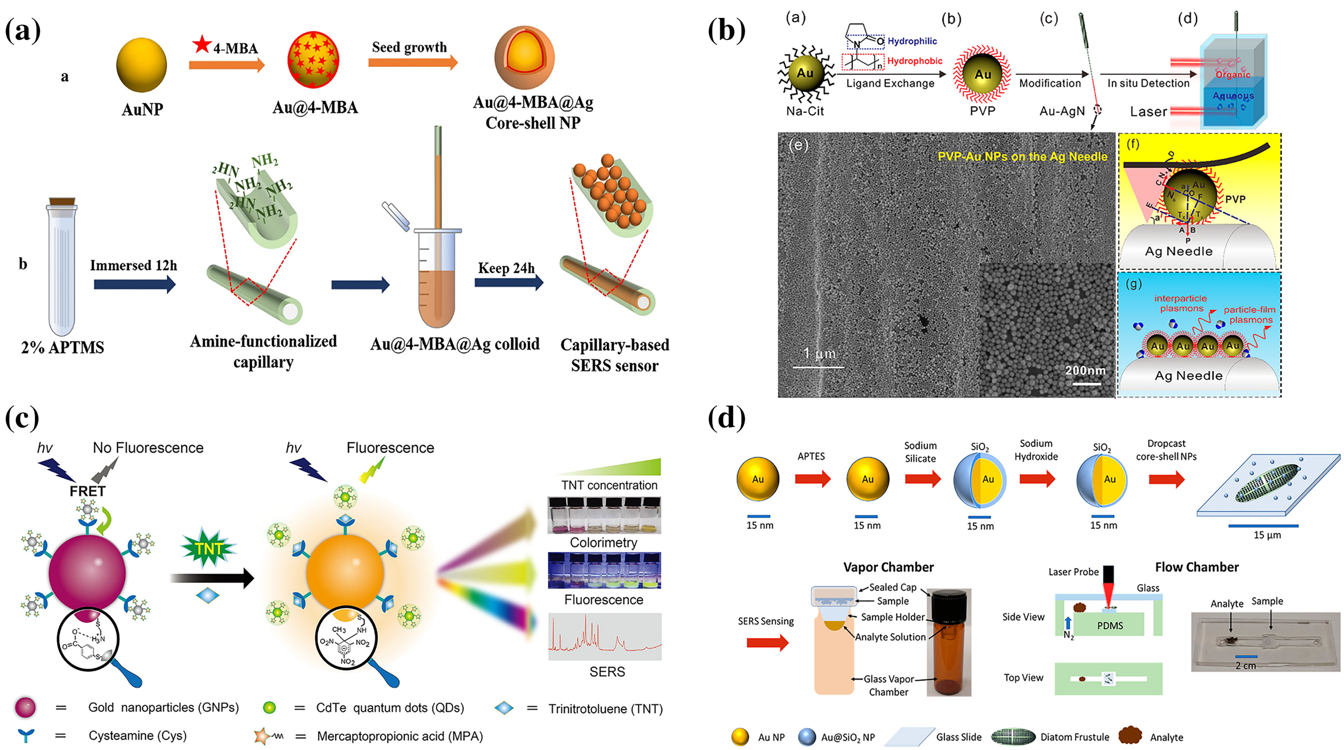

FIGURE 1 (a) A schematic diagram of fabrication of capillary-based SERS sensor. (b) Schematic representation of the fabrication and detection process of the portable Au-AgNP sensor. (c) Schematic illustration of tri-mode sensing platform for TNT analysis enabled by AuNPs-QDs assemblies. (d) Schematic showing synthesis process of $Au@SiO_2$ core-shell nanoparticles and subsequent integration on frustule-populated substrate to form multiscale SERS vapor sensor and integration with stagnant vapor and vapor flow chambers. Adapted with permission from references,[55,67,81,82] copyrights 2021 Springer Nature, 2018 American Chemical Society, 2020 Elsevier B.V., 2020, American Chemical Society.

used increasingly to prevent and treat various diseases in fish with the rapid development of aquaculture. However, using fungicides and repellents has risks to a certain extent, for instance, MG and CV need more time to degrade, and have certain genotoxicity, MB can cause adverse effects on human health, such as vomiting, shock and quadriplegia.[68–70] Therefore, there is an urgent need to establish a fast, simple and portable method that can recognize and monitor multiple dyes simultaneously.

A porous filter paper decorated with nanoparticles was designed to determine R6G powder in the air. The porous fibrous structure facilitates the capture of the R6G powder by the vacuum filter, and the separation of the components by paper chromatography, meanwhile, the nanoparticles were applied to enhance the SERS signals. The determination accuracy at R6G levels was as low as 0.6 mg/m^3.[71] When the analyte droplets are dropped on the dry substrate, the molecular distribution on the substrate may suffer from non-uniformity problems due to the coffee ring effect, resulting in a loss of uniformity and sensitivity. Zhang et al developed the single and dimer particle-nanosensors as SERS substrates. Moreover, the LOD of CV molecules was as low as femtomolar or attomolar levels for detecting various dye molecules, e.g., R6G, rhodamine B, and MG.[72] However, owing to the actual samples always being complex multiphase heterogeneous materials which consist of oil and aqueous phases, it is difficult to test actual samples rapidly, effectively on-site by SERS. To solve the problem, Yang and coworkers constructed a SERS sensor to recognize target molecules in multiphase heterogeneous samples, based on the composition of commercial Ag acupuncture needle and polyvinyl-pyrrolidine gold nanoparticles (PVP-AuNPs) (Figure 1b). The sensor was able to monitor diverse target molecules dissolved both in the organic and aqueous phase synchronously, such as MG and lemon yellow in aqueous, and thiram and sole 2,2′-bpy in organic phase.[73] Lin et al constructed a capillary SERS substrate with a tiny orifice, which has the ability to achieve effective and lossless sample extraction. They assembled core-shell nanorods (Au@4-MBA@AgNRs) onto the inner wall of the capillary, while 4-mercaptobenzoic acid (4-MBA) was used as the internal standard molecule. Then the sensor can be used for highly sensitive quantitative analysis of fungicides on shells.[74]

AO II, a non-food coloring, is prohibited from being added to foodstuffs. Excessive consumption may lead to food poisoning, long-term consumption or even cancer. However, due to its bright color and low price, some unscrupulous traders prefer to add it to the processing of chili powder for huge profits, which seriously endangers the health of consumers. Wang et al developed a SERS sensor for the determination of AO II by decorating amino-functionalized Cr-based metal organic frameworks on AuNPs (NH_2-MIL-101[Cr]@AuNPs). The sensor exhibited high selectivity and high adsorption performance with a lower LOD of 0.05 mg/L and a wide detection range of 0.05–50 mg/L.[75]

3.1.3 | Determination of organic pollutants

Benzene, toluene, ethylbenzene and xylene (BTEX) are typical organic pollutants discharged from industrial wastes, which are harmful to human health and ecological environment. Long-term exposure to BTEX can cause serious damage to the skin, respiratory system and central nervous system. Therefore, it is essential to develop accurate and effective strategies for on-site analysis of organic pollutants without purification, capture and identification.

Jung et al modified hydrophobic hexagonal boron nitride (hBN)-coated silver nanowires (AgNWs) on sponge materials for identification and determination of organic pollutants. The sponge material can enrich the organic pollutant molecules. The AgNWs coated with hBN can generate good SERS signals to detect the target molecules through hydrophobic and π-π interactions. Furthermore, this method can identify binary and ternary mixtures of BTEX by comparing the Raman spectra of the components in the mixtures.[76]

Volatile organic compounds (VOCs) are a severe threat to human health, and long-term exposure may cause neurological disorders, even cancer. However, VOCs are difficult to detect due to their volatility. Surface modifications of absorbent materials on sensor surface are used for on-site Raman measurements. Zhang et al fabricated a SERS sensor by decorating AgNPs on the mesoporous silica gel which can exhibit ultralow detection of VOCs including toluene (68 ppm), benzene (56 ppm), chloroform (129 ppm), and acetone (161 ppm) with a portable Raman spectrometer.[77]

Polycyclic aromatic hydrocarbons (PAHs) are well known to be a class of toxic carcinogens that are emitted from wildfires. Li et al prepared a wearable SERS array sensor for on-site environmental PAHs SERS monitoring by sticking Ag/MoS_2 ink on fire-retardant fiber gloves using screen printing with an adhesive agent. Three kinds of PAHs (naphthalene, anthracene, and pyrene) were monitored by the wearable sensor and a portable Raman spectrometer.[78]

By combining with a portable Raman spectrometer, the researchers also established SERS methods for the detection of organic pollutants such as dimethyl phthalate,[79] formaldehyde,[80] melamine,[81] cyanide,[82] azide,[83] etc.

3.1.4 | Determination of explosives

2,4,6-Trinitrotoluene (TNT), a military-grade explosive that not only pollutes the environment but also threatens public safety, remains a major global concern. There are many examples of SERS detection of trace explosives with portable Raman spectrometers.[84,85] Although colorimetric tests were used to detect explosives as the most common methods, which is fast and portable, they often exhibit false positives and lack sensitivity. A colored Janowsky complex was formed based on nitroaromatic explosives and the enolate ion of 3-mercapto-2-butanone. Based on this principle, Graham and coworkers demonstrated a SERS probe which has a thiol functional group that allows covalent attachment to the surface of AgNPs. This method can specifically capture explosive molecules, avoid false positives, and improve the sensitivity.[86] Ren and coworkers presented a multimode sensing approach for on-site determination of TNT in complex matrices based on AuNPs-QD (quantum dot). The strategy can have good performances in colorimetric, fluorescence and SERS (Figure 1c). In these three channels, SERS channel has the lowest concentration for TNT (3.2 fM). Besides, by combing with a portable Raman spectrometer, the method enables quantitative analysis of TNT from real samples such as soil, wine, fruit, and clothing.[87] Wang and coworkers integrated diatom photonic crystals and gold-silica core-shell nanoparticles to detect TNT vapors. The detection time was as low as 3 min and the detection sensitivity could be as low as 1 ppm (Figure 1d).[88]

In addition to the earlier environmental pollutants, portable Raman spectrometers can also be used for rapid analysis of chemical warfare agents (CWAs) and pathogens in the environment. It remains a challenge for on-site SERS applications to detect gaseous chemicals with small cross-sections. To solve this problem, Mallada and coworkers prepared a thin film which consisted of core-shell Au@AgNRs within a zeolitic imidazolate framework-8 (Au@Ag@ZIF-8). ZIF-8 can trap the dimethyl methylphosphonate (DMMP) or 2-chloroethyl ethyl sulfide (CEES) from the gas phase, while Au@AgNPs can provide SERS hotspots and amplify the Raman signal. The method can detect DMMP in ambient air (2.5 ppm) in 21 s, and CEES in nitrogen (76 ppb) in 54 s.[89]

3.2 | Agricultural pollutants

Agricultural pollutants are harmful components that threaten the human health, environment and ecosystems. Common agricultural pollutants include pesticides, veterinary drugs, mycotoxins, bacteria, illegal additives, and viruses, etc. The development of agricultural pollutants detection methods with high sensitivity and selectivity is still required. Although molecular and chromatographic techniques have high sensitivity, they are limited by the large size of the instruments and are not suitable for outdoor on-site detection.[90–92] However, SERS technology can combine with portable detection spectrometers and provide unique information about the analytes in a short time.

3.2.1 | Determination of pesticide residue

Pesticides are important agricultural production materials for preventing, eliminating and controlling insects, grasses and other harmful organisms which are harmful in the production process of agricultural products.[93–95] The pesticides used in the production of agricultural products are mainly divided into four categories: organochlorine, organophosphorus, carbamate and pyrethroid pesticides. However, pesticide residues will pollute environmental water, soil, and atmosphere, etc. Moreover, most pesticides are highly toxic, carcinogenic and teratogenic, and can cause a variety of diseases and even death after entering the human body. SERS has been increasingly applied to the detection of pesticide residues in recent years.[96–98]

Benzyladenine (6-BA) is a plant growth regulator widely used on fruit trees and horticultural crops at all stages from germination to harvest.[99,100] Excessive intake of 6-BA, however, is harmful to the human health, causing nausea and vomiting. Wang et al prepared AgNPs by a chemical reduction method as SERS substrates for the determination of 6-BA. Owing to the fact that 6-BA exhibits obvious SERS signals, they investigated the effects of type of aggregation agent, pH of buffer solution, concentration of AgNPs, mixing time and

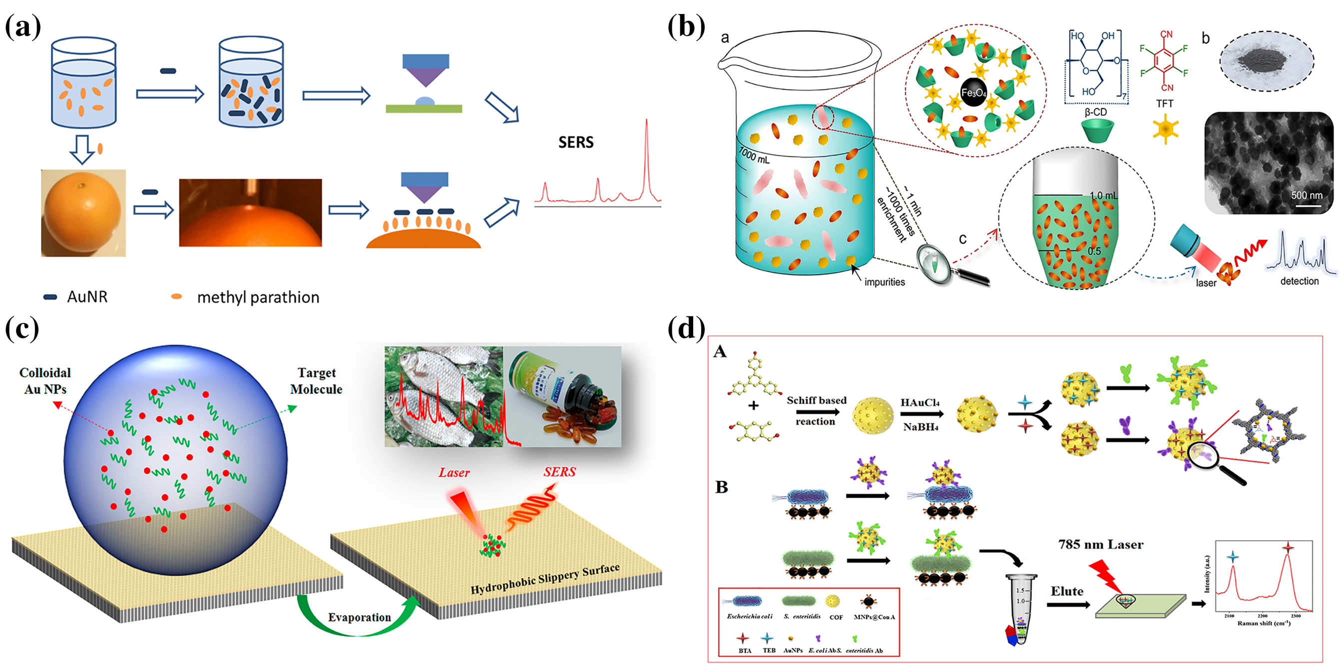

FIGURE 2 (a) Scheme of AuNRs-based casting-and-sensing SERS platform for rapid and fingerprinting detection of methyl parathion in solution and on the surface. (b) Schematic of the current enrichment and detection based on the porous β-cyclodextrin polymer. (c) Schematic illustration of the SERS detection based on hydrophobic slippery surface. (d) Schematic illustrations of the preparation procedure of novel COF based Raman tags and the interaction between TBDP and Raman reporters/antibody. Adapted with permission from references,[91,95,107,108] copyrights 2019 Elsevier B.V., 2021 Springer Nature, 2019, American Chemical Society, 2022 Elsevier B.V.

reaction and concentration of 6-BA. Under optimal conditions, the LOD was as low as 3.3 μg/L.[101] Hou and coworkers designed a SERS strategy for the determination of methyl parathion (MP) residue on the fruit and leave surfaces via directly dropping colloidal AuNRs (Figure 2a). And the sensor was further used to monitor the MP in lake water by a portable Raman spectrometer. The sensor can realize the MP analysis with a LOD of 1 μM in spiked lake water and 110–440 ng/cm^2 on the surface of various fruits and plant leaves. These results indicate that the method has potential to determine MP residue in real application.[102] A SERS sensor was developed based on bipyramid gold nanoparticles (BP-AuNPs) decorated on tape for the determination of MP residues. The pesticides residues on the surface of fruits and vegetables can be collected by a 'paste and peel off' method with a commercial tape. After collection, BP-AuNPs colloids were dropped on the tape and the SERS testing was performed. The method was further applied to determine MP in samples such as apples, cucumbers and tomatoes with a LOD at ng/cm^2 level.[103]

A SERS probe was demonstrated by growth of MOF-5 film on the 2D SERS substrate for quantitative analysis of organophosphorus pesticides in a soil matrix. The as-prepared SERS substrates are not only cheap, but also can combine with portable Raman spectrometers for actual application. And the LODs are down to 10^{-12} M.[104] Chang et al manufactured a hard SERS substrate by spin-coating a silver nanopaste (AgNPA) on a commercially electrode material. Silver nanocracks (AgNCKs) with small gaps could be generated on silicon wafers via the spin-coating process which provide abundant hotspots area for SERS testing. AgNCK arrays combined with a portable 785-nm Raman spectrometer have the ability to determine three pesticide residues with high sensitivity and selectivity. A dithiocarbamate (thiram) and two organophosphates (dimethoate, organophosphates) were detected, and the LOD for thiram was as low as 52 ppb, the LOD for dimethoate was as low as 0.66 ppb, and the LOD for methamidophos was as low as 2.1 ppb, respectively.[105] Fang and coworkers developed an enrichment-typed SERS strategy based on a mesoporous nanosponge consisting of magnetic nanoparticles modified with porous β-cyclodextrin polymers (Figure 2b). Furthermore, it showed remarkable ability to remove the organic micropollutants effectively and rapidly. The LODs for organic pollutants detection can be improved by 2–3 orders significantly.[106]

3.2.2 | Determination of veterinary drug residue

Veterinary drugs have played a positive role in reducing the morbidity and mortality of livestock and poultry, promoting growth, and improving product quality, and have been widely used in livestock production. At present, there are various veterinary drugs used in animal husbandry and production, including: chloramphenicol,[107] quinolones,[108] sulfonamides,[109] etc. Veterinary drugs are metabolized and absorbed by animals, accumulate in animals, and have direct toxic effects on humans. If humans eat animal-derived foods containing antimicrobial drug residues for a long time, they will also develop certain drug resistance to the drugs, causing allergic reactions and even anaphylactic shock. In order to ensure the ecosystem, it is necessary to develop rapid, accurate and cost-effective on-site detection methods for veterinary drug residues in food and environment.

Neomycin (NEO) and quinolones (QNS) are antibiotics that are widely used by veterinarians to treat bacterial infections in animals due to their potent inhibition of both Gram-positive and Gram-negative bacteria.[110] Zhang et al. described a SERS-FLA method for the determination of NEO and QNS simultaneously. The method consisted of two immuno-nanoprobes that captured the two antibiotics (NEO and QNS) respectively. One of the two immuno-nanoprobes consisted of AuNPs modified by the Raman reporter 4-aminothiophenol (PATP). Another consisted of AuNPs modified by monoclonal antibody against NEO or NOR (NEOmAb or NORmAb). By capturing the PATP-AuNPs in the test line of a lateral flow assay (LFA), NEO and QNS can be monitored by SERS testing. And the LODs was as low as 0.37 pg/ml for NEO and 0.55 pg/ml for QNS, respectively.[111]

Sulfapyridine is largely employed as a veterinary drug. The consumption of food containing sulfapyridine residues can cause certain harm to the human health. Ríos and coworkers developed a SERS strategy for quantitative analysis of sulfapyridine with a portable Raman spectrometer. The SERS substrate was fabricated with multi-walled carbon nanotubes (MWCNTs) and AuNPs without any functionalization. And the concentration range of the strategy was 10–100 ng/ml.[112]

Since ciprofloxacin (CIP) is an effective antibiotic which can be used to treat bacterial infections. Therefore, it is critical to develop sensitive and accurate methods to detect CIP in environment. Spherical and triangle nanoparticles were prepared by femtosecond laser as SERS substrates for the determination of CIP. Under the action of nanosecond laser, the shape of the nanoparticles changes from hexagonal to spherical. The spherical-hexagonal AuNPs self-assembly morphology was formed (the average diameter: 6 nm). The different shapes of AuNPs can achieve the determination of CIP in water and milk, and the LOD was 7.5×10^{-8} M.[113]

3.2.3 | Determination of illegal additives, pathogenic bacteria and biotoxins

Illegal additives refer to the presence or excessive use of legally prohibited substances in agricultural products and livestock. Unscrupulous merchants use deceptive means to add these illegal additives to increase the content of certain nutrients and preserve freshness.[114–116] Illegal additives include diethylhexyl phthalate (DEHP) in energy drinks, sodium hexametaphosphate (HP) in tea water sample, and morphine in a chafing dish. Developing simple and on-site methods to detect illegal additives can reduce the risk of consumer victimization.

HP, a common food quality improver, can increase the moisture content of meat and prevents fat oxidation. However, excessive HP will not only destroy the nutritional content of food, but also endangers human health if it accumulates over a long time. Jiang et al. prepared a SERS probe of an orange-red silver nanochain (AgNC) sol synthesized with $AgNO_3$ and hydrazine hydrate. The probe was synthesized by modifying rhodamine S (RhS) cationic dye on AgNCs. SERS intensity at 1506 cm^{-1} decreased directly with the addition of the HP. The method has a linear correlation range of 0.0125 to 0.3 μM with a LOD of 6 nM.[116] DEHP is a plasticizer and is toxic to human reproductive organs. Long-term intake of this substance increases the risk of liver cancer and breast cancer. A SERS strategy for the quantitative analysis of the DEHP residue in energy drinks was developed based on hexakisphosphate (IP6) modified Au@AgNPs (Au@Ag@IP6). After modifying 1-dodecanethiol, DEHP molecules were captured near SERS hotspots area. The strategy can analyze DEHP as low as 10^{-8} M.[117] A SERS substrate was developed to detect the illegal additive by infusing perfluorinated fluid into the hydrophobic polytetrafluoroethylene membrane. The analytes were enriched and delivered to the specific sites based on a hydrophobic slippery surface which can eliminate the diffusion process during droplet evaporation. The pinning-free substrate was applied to the determination of morphine in a hot pot, and the LOD was 0.05 ppm (Figure 2c).[118]

Pathogens seriously threaten public health and cause foodborne diseases. Among them, foodborne pathogens are the most critical. Therefore, a SERS immuno-sensor based on multifunctional covalent organic frameworks (COFs) was developed for the quantitative analysis of foodborne pathogens in food samples. When target bacterium was added, both the magnetic material and the Raman tag work together to identify it. After capturing the target bacterium, it can be easily separated from the matrices using an external magnet. The sensor was biologically interference-free, highly selective and sensitive. And it was further applied to detect *Escherichia coli* and *Salmonella enteritidis* in milk samples with the LOD of 10 CFU/ml (Figure 2d).[119] The water activity of low moisture foods (LMFs) is usually lower than 85%. Bacteria can survive for a long time under such conditions. However, once LMFs containing live bacteria are consumed, they may cause food-borne illness and endanger health. A Dual Immunological Raman-Enabled Crosschecking Test (DIRECT) was developed for LMFs with a portable Raman spectrometer. It can detect bacteria within 30–45 min with LODs as low as 102 CFU/g.[120]

Marine biotoxins are highly toxic metabolic components in marine organisms, which can accumulate in mollusks and threaten human health. Therefore, it is critical to develop reliable and rapid methods for detection of marine toxins in seafood. Pinzaru et al designed a micro-SERS technique based on AgNPs for the determination of marine toxins. The SERS method can detect extremely small amounts of biotoxins such as okadaic acid. And the LOD of this method is 0.81 nM in acid form or as dissolved potassium salt.[121] Aflatoxins (AFs) are widely found in improperly stored peanuts, soybeans, and wheat. Ingestion may lead to acute liver injury, cirrhosis, and other diseases. A thin layer chromatography (TLC)-SERS method was proposed for on-site analysis of AFs in moldy agricultural products. AuNPs were chosen as substrates to provide the SERS hotspots to enhance the SERS signals. Four different AFs were separated by TLC, while SERS signals were collected by a small portable Raman spectrometer. TLC-SERS method was applied to AF on-site analysis and LOD was as low as 1.5×10^{-6} M for AFB_1, 1.1×10^{-5} M for AFB_2, 1.2×10^{-6} M for AFB_2, 6.0×10^{-7} M for AFG_2.[122]

3.3 | Biomedical analysis

3.3.1 | Determination of drugs

The safe use of drugs is significantly to ensure the safety of human health and the environment. However, with the continuous increase in the variety and dosage of drugs, the irregularity of drug production and excessive drug use have posed a serious threat to human health.[123,124] The development of drug testing technology plays an important role in improving drug safety and improving quality of life. In recent years, the development of sensitivity, stability, real-time, and trace detection of drug detection has attracted more and more researchers' interest.[125–127]

The falsification of antimalarial pharmaceuticals has negative influence on the public health. A SERS strategy was developed to measure the active pharmaceutical ingredients in falsified antimalarial pharmaceuticals drugs, such as pure chloroquine, primaquine, and doxycycline.[128] Propylthiouracil (PTU) and methimazole (MTZ), which are thiourea antithyroid drugs, can treat hyperthyroidism because they inhibit thyroid hormone production. However, they can cause side effects such as cutaneous vasculitis, acute liver oxidative damage, interstitial pneumonia, and other diseases. Tian and coworkers developed a SERS approach for the quantitative analysis of PTU and MTZ by a portable Raman spectrometer. They prepared SA-AgNPs as SERS substrates. The atoms of sulfur and nitrogen of PTU and MTZ can have strong interaction with AgNPs to produce SERS signals. PTU and MTZ were detected in actual samples, and the LODs were 1.58×10^{-10} M (for PTU) and 2.97×10^{-11} M (for MTZ).[129]

A portable 3D-printed paper cartridge was constructed to preconcentrate and detect drugs by a portable Raman spectrometer. AgNWs were decorated on the paper tip as SERS substrates in the enclosed environment. In addition, preconcentration and detection can be achieved in a 3D-printed cartridge for just one dollar. The analysis time process required less than 1 h, including sample pretreatment and preconcentration, drying, SERS measurements, and quantification analysis. The cartridge further was applied to determine epirubicin hydrochloride in human serum (LOD was 3×10^{-6} M).[130]

Fentanyl is a class of opioids widely used as an anesthetic analgesic for the treatment of cancer and surgical analgesia. Excessive use can be addictive and lead to a series of side effects, such as nausea and vomiting, lethargy, and dyspnea. Not only is fentanyl cheap and easy to transport, it is also a more powerful anesthetic compared with the other two drugs (heroin and morphine). A capillary-based SERS platform was proposed for the determination of fentanyl in serum. AuTOH was coated on capillary to obtain the SERS signals. And the platform was applied to detect fentanyl with a LOD as low as 1.86 ng/ml (in aqueous solution) and 40.63 ng/ml (in serum samples).[131]

Methylene dioxymethamphetamine (MDMA) and methamphetamine (MAMP) have become the most widely circulated drugs due to their easy synthesis, low cost and strong addiction. Drug abusers are usually identified by detecting drug substances in blood, urine and saliva. Weng et a. developed a SERS method for the analysis of MAMP in urine based on methoxypolyethylene glycol thiol coated AuNRs. This method does not require sample pretreatment and uses a portable Raman instrument, which is more suitable for on-site application. And MAMP concentrations of 0.4, 3, and 30 ppm were detected in urine samples from drug abusers.[132]

3.3.2 | Determination of biomarkers

Biomarkers refer to biochemical indicators that can reflect the possible changes in organ, tissue, cell and subcellular structure or function or may change, such as nucleic acids,[132] proteins,[133,134] enzymes,[135,136] hormone,[137] active molecules,[138,139] and circulating cells found in the body,[47] etc. Biomarkers are often used for disease diagnosis and classification, to judge disease stage, development and severity, or to evaluate the safety and effectiveness of new clinical drugs or new treatments, as well as to predict individual disease risk and clinical screening of high-risk groups, etc. Biomarkers have important clinical significance, but their detection is often difficult due to their presence in complex matrices, large background interference, and low content. Therefore, multiplex and selective detection of several biomarkers is important for comprehensive screening test of cancer.

Nucleic acid-based diagnosis is crucial in medical diagnosis with high specificity and sensitivity. Family susceptibility genes can be found through nucleic acid diagnosis, and zero-level prevention can be performed to delay the occurrence of clinical symptoms. Ngo et al proposed a SERS strategy for detection of pathogen RNA in blood lysate directly with a 'lab-in-a-stick' portable device. Plasmodium falciparum malaria parasite RNA was directly detected in infected red blood cells lysate with a LOD of 200 fM.[140] Currently, nucleic acid lateral flow sensing has attracted extensive attention of researchers with the advantages of being accurate, rapid, and cost-effective. A lateral flow SERS platform was fabricated to recognize microRNA-21 based on a catalytic hairpin assembly signal amplification strategy. Numerous double-stranded DNAs were formed after adding microRNA-21 resulting in the exposure of the biotin groups. The Au@Ag nanoprobes with exposed biotin can be captured on the test line via its interaction with streptavidin. The strip is then scanned to obtain a SERS spectrum by a portable SERS spectrometer. And the LOD of microRNA-21 was as low as 84 fM.[141]

Mucin-1 is a disease marker for breast cancer and pancreatic cancer for clinical diagnosis. Kang and coworkers prepared a paper-based SERS test strip for the determination of mucin-1 in whole blood samples. The AuNPs were *in situ* synthesized on the paper fibers to

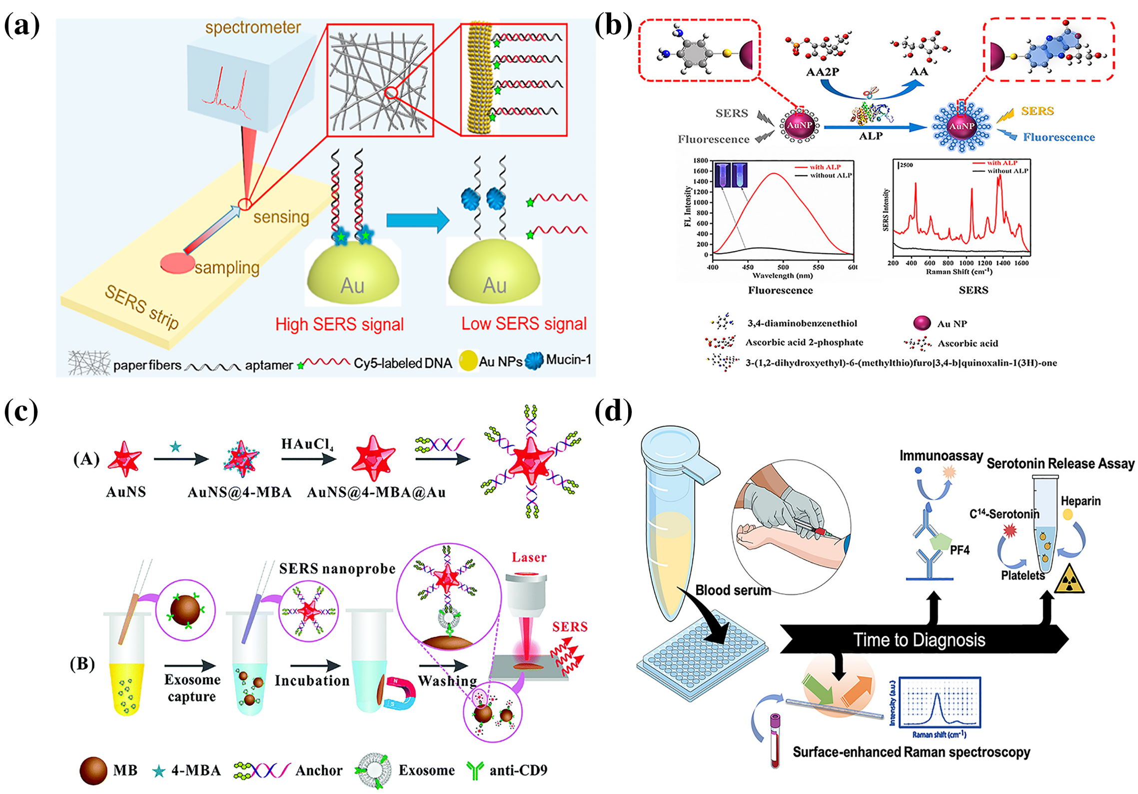

FIGURE 3 (a) Concept and design of the paper-based SERS test strip. (b) Schematic illustration for the determination of ALP activity based on the ALP-triggered OPD(S)-AuNPs reaction with AA. (c) Sequential SERS-based assay process for the detection of exosomes. (d) Schematic showing the various assays used for the diagnosis of HIT. Adapted with permission from references,132,135,137,138 copyrights 2017 Elsevier B.V., 2021 Elsevier B.V., 2018 Royal Society of Chemistry, 2020 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

generate hot spots and enhanced the size exclusion effect. This SERS test strip can be applied in combination with a portable spectrometer, and the test process is fast, convenient and accurate and has become a potential tool for clinical analysis (Figure 3a).[142]

Carcinoembryonic antigen (CEA) and α-fetoprotein (AFP) are two common biomarkers of liver and colon cancer. A vertical flow microarray chip is prepared for the determination of AFP and CEA based on core-shell SERS nanotags and porous nitrocellulose. AFP and CEA were detected according to the difference of the specific Raman band at 592 cm^{-1}. The linear ranges were 0.1–10 μg/ml for both AFP and CEA, and the LOD was 0.27 pg/ml for AFP, 0.96 pg/ml for CEA.[143]

As a potential biomarker of malignant tumors, high level of hyaluronidase (HAase) is associated with bladder cancer. HAase is involved in numerous physiological processes such as fertilization, cell adhesion, wound healing, and tumor growth. A SERS method was developed for the determination of HAase based on hyaluronic acid-coated gold nanoparticles (HA-AuNPs). Wang et al synthesized AuNPs coated with hyaluronic acid (HA) by a one-pot method as SERS substrates. HAase can hydrolyze HA into oligomers which leads to the destruction of the SERS substrates. These oligomers can increase the surface shielding of AuNPs. Under the optimized experimental conditions, the LOD for HAase was 0.4 mU/ml. The method was applied to real samples (such as human urine) with a portable Raman spectrometer, and the recoveries of HAase ranged from 97.2 to 103.9%.[144] On the basis of this, Wang et al developed a SERS-fluorescent dual-mode platform for the quantitative analysis of alkaline phosphatase (ALP) in human serum. ALP as an important biomarker is closely associated with various diseases. The development of sensitive ALP assay can play an important role in the clinical diagnosis of ALP-related diseases. It is reported the ALP can trigger the *in situ* reaction between o-phenylenediamine (OPD) and AA. Wang et al prepared a SERS sensor by connecting 3,4-diaminobenzene-thiol on the surface of AuNPs through an Au–sulfur covalent bond. The increased SERS intensity correlated linearly with ALP concentration in the range 0.5–10 mU/ml, with a LOD of 0.2 mU/ml. (Figure 3b).[145]

Human chorionic gonadotropin (hCG) is an important clinical biomarker which is closely associated to some diseases, such as gestational trophoblastic disease and Down syndrome. The hCG levels of pregnant females are higher than normal in serum and urine, thus the detection of hCG is of great significance for early pregnancy diagnosis. A rapid SERS-LFA method was presented to detect hCG with a fiber optic probe. The method achieved rapid quantification of hCG in human urine samples within 2–5 s, which is shorter than the other SERS methods by large and expensive Raman instruments. The sensitivity of the SERS-LFA sensor for hCG is 15-times more than the gold standard, which is satisfactory for real application and point-of-care testing (POCT).[146]

As important signaling molecules, exosomes carry a variety of proteins, microRNAs and lipids, which can be used as biomarkers of cancer. A SERS method was developed for specific isolation and accurate quantification of exosomes with a portable Raman spectrometer. Yin et al demonstrated the modification of AuNS@4-MBA@Au nanoshell structures on a bivalent cholesterol-labeled DNA anchor which can be used as SERS nanoprobes. Exosomes are specifically captured by combining immunoaffinity, and then SERS nanoprobes are fixed on the surface of exosomes by hydrophobic interactions between cholesterol and lipid membranes, thus forming a sandwich-type immunocomplex (Figure 3c). The SERS signals are positively correlated with the exosome concentration with a linear range of 40 to 4×10^7 particles per microliter with the LODs down to 27 particles per μl.[147]

Heparin is commonly used to treat thrombotic disorders such as acute coronary syndromes because it can reduce thrombus formation. However, improper use can lead to serious side effects, such as limb ischemia and gangrene. Barman and coworkers proposed a SERS-capillary platform for the detection of heparin. The sensing platform was fabricated with Ag-ink coated tube (Figure 3d). The strategy achieves highly sensitive detection of heparin from a total of 34 post-operative patients, 11 of who were confirmed to be HIT-positive through gold standard functional assays.[148]

Glutathione (GSH) is a naturally synthesized peptide in human cells. Reduced GSH and oxidized glutathione (GSSG) are the main components of the system for maintaining intracellular redox homeostasis. GSH was the main active state, accounting for about 95%, while GSSG accounts for about 1% in the inactive state. They remain relatively stable but could be altered under abnormal physiological conditions. Xie and coworkers prepared a SERS method to detect GSH and GSSG concentrations with a portable SERS spectrometer. The detection mechanism is based on that 5, 5′-dithiobis-(2-nitrobenzoic acid) (DTNB) can initiate the reduction of GSH and convert to 2-nitro-5-thiobenzoic acid (TNB) which has a strong SERS signal. The LOD was 10 nM both for GSH and GSSG.[149]

Circulating cancer-derived small extracellular vesicles (EVs) are an important biomarker for cancer diagnosis and drug therapy monitoring in liquid biopsy. It is nanoscale membranous vesicles shed from cancer cells, DNA and proteins for cell-to-cell communication. Wang and coworkers developed an effective strategy to simultaneously profile multiple protein biomarkers expressed on cancer derived small EVs without complex isolation steps. Rapid and multiplexed phenotypic profiling of small EVs is achieved by mixing specific detection antibody-coated SERS nanotags, filtered conditioned EV-suspended medium (conditioned EVs), and capture antibody (CD63)-conjugated magnetic beads to form a sandwich immunoassay.[150]

3.3.3 | Determination of virus and bacteria

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the specific pathogen of the 2019 coronavirus disease (COVID-19) which has impacted humans worldwide for over 2 years now. Common symptoms of SARS-CoV-2 infection include fever, cough, and dyspnea. Infection severely can lead to pneumonia, severe acute respiratory syndrome and even death. The SARS-CoV-2 is highly contagious and can spread easily through aerosols, respiratory droplets, and direct contact with body surfaces. Thus, the outbreak of the epidemic can be effectively controlled by diagnosis of the suspected cases rapidly. Wang and coworkers developed a biosensor to monitor anti-

SARS-CoV-2 IgM/IgG combined SERS with lateral flow immunochromatography assay (LFIA) in clinical samples. Functionalized SiO_2@AgNPs were integrated into the LFIA system as dual-layers advanced SERS tags. They detected 68 clinical serum cases (19 positive and 49 negative cases), indicating the potential and ability of the constructed biosensor in clinical analysis.[151] On this basis, a SERS-based immunoassay method was constructed for the analysis of SARS-CoV-2 involving an antibody pair, hollow AuNPs, and magnetic beads. The hollow AuNPs were used as SERS substrates to produce strong SERS signals, while the antibody pair against the SARS-CoV-2 antigen and magnetic beads were used to capture SARS-CoV-2. LODs was 2.56 fg/ml for the SARS-CoV-2 antigen.[152] Zhang et al combined SERS with multivariate analysis to establish a strategy for the determination of SARS-CoV-2 with a portable Raman spectrometer. No preprocessing steps are required in this assaying with an ultra-fast way. The assay was applied for the on-site detection of SARS-CoV-2 in 23 water samples extracted from sewage treatment plants to prove its applicability for SARS-CoV-2 detection. In addition, the virus decay process in the sewage treatment plant was further explored and SARS-CoV-2 in the pipe network was tracked.[153]

In the past decades, avian influenza virus (AIV) has been widely spread around the world. Once a human is infected with AIV, it can cause severe disease because it spreads easily among poultry and humans. The outbreaks and epidemics of AIV seriously threaten human health and the global economy. Xiao et al have developed a SERS-LFIA approach for the determination of AIV H7N9 based on core-shell nanoparticles ($AuAg^{4\text{-}ATP}$@AgNPs). The modification of the silver shell can effectively avoid the aggregation of nanoparticles in the T line and C line, thus significantly improving the stability of $AuAg^{4\text{-}ATP}$@AgNPs composite. By observing the color change of the test line, the presence of the target analytes and the amount of virus represented by the hemagglutination titer of AIV H7N9 can be visually resolved.[154]

Escherichia coli is the most important and abundant bacterium in humans and in many animals. *Escherichia coli* may cause severe diarrhea and sepsis under special circumstances, such as reduced immunity and long-term lack of intestinal stimulation. Choi and coworkers constructed a strategy for the identification of subtyping *E. coli* colonies clinically relevant human blood-cultured. Seven *E. coli* isolates was identified by prepared gold-deposited SERS substrates. The strategy achieved a rapid process time of 30 min, which includes a drying time of 20 min on the SERS substrate with a high reproducibility of 5%. An enhancement factor was obtained of 1.6×10^4 to Raman intensities.[155]

3.4 | Other fields

3.4.1 | Forensic application

The blood at the scene of the crime contains many secrets, such as identifying the perpetrator and the victim, understanding the process of the crime, and estimating the time of the crime. The development of simple, rapid, portable and accurate blood analysis and identification technologies can provide investigators with more accurate information and allow more time for subsequent activities. A SERS procedure for the detection of dried blood stains was developed in the forensic field. And the method allowed high-quality SERS spectra to be observed from blood stains diluted up to 10^5-fold.[156]

Gunshot residue (GSR) evidence is used forensically to determine whether a firearm was discharged. Typically, GSR is exclusively identified by its morphology and the presence of lead, barium, and antimony measured by scanning electron microscopy with energy-dispersive X-ray spectroscopy (SEM–EDX). However, the SEM–EDX instrument is large and expensive, and professional training personnel are required to perform the measurement. SERS technology can achieve an accurate and selective determination of GSR using portable Raman devices. Thayer et al developed a SERS method for the detection of GSR using a portable Raman spectrometer. Diphenylamine (DPA) and ethyl centralite (EC) can be used to make explosive stabilizers. The LOD was 197.8 mM for DPA and 123.6 mM for EC in acetone, acetonitrile, ethanol, and methanol.[157]

3.4.2 | Art and cultural heritage materials application

The identification and characterization of binders in art and cultural heritage materials provide critical information for dating, authentication, and conservation. A strategy for the analysis of proteinaceous binders was developed with silica film and AgNPs. The silica film was fabricated with silica sol deposited on the germination paper, and AgNPs were used as SERS substrate to obtain the SERS signals. And the minimum detectable concentration of bovine serum albumin in the paint models was 0.005% (w/w).[158]

4 | CONCLUSION AND OUTLOOK

SERS technique is a developing but promising technique which has great potential for providing sensitive, rapid, and 'fingerprint-like' details about structure informative detection. The continuous development of nanostructured SERS substrates and portable Raman spectrometers has propelled SERS technology to play an important role in future rapid field detection, making it a fast, ultrasensitive, accurate, and cost-effective analytical technique. However, it still has some challenges as the same as any analytical technique.

1. Substrates simplification. Although various SERS-active substrates with high sensitivity and high enhancement performance have been developed, the stability of SERS substrates are still critical issues. Researchers are increasingly tending to develop SERS substrates that are simple to manufacture, cost-effective, have high-activity and easy to transport and store.
2. Instrument miniaturization. With the development of small portable Raman devices, the application of SERS technique is no longer

limited to large-scale Raman devices. At present, the portable Raman spectrometers on the market are relatively expensive, which is not conducive to popularization. While improving the sensitivity of the instrument, the size of the device should be further reduced. In addition, the laser excitation wavelength of the portable Raman system should cover a wider range (from the visible to near infrared range) to meet field and real-time tests in different fields.

3. Targets diversification. SERS technology has limitations for the detection of analytes in complex samples. SERS will show the low-sensitivity results of complex samples with no pretreatment in detecting process. Some interactions and interference will directly limit the delivery of analytes to the nano-metal surface which influence the speed, sensitivity, and robustness of the method. To solve this problem, SERS can be combined with diverse technologies to enhance detection capability, including chemical separation techniques, biological capturing techniques, colorimetric techniques, and microfluidic techniques. In addition, the combination of SERS and other analytical techniques can complement the advantages and remedy the defects of each technique to achieve more accurate and multi-dimensional characterizations.
4. Convenient operation. With the diversification of detection locations and detection methods for portable Raman measurements, the requirements for operating steps are becoming more and more convenient. Researchers are pursuing simple and fast preparation steps for SERS substrates with high stability and rapid and sensitive detection of targets.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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REFERENCES

[1] P. J. Hendra, M. Fleischmann, A. J. Mcquillan, *Chem. Phys. Lett.* **1974**, *26*, 163.
[2] D. L. Jeanmaire, R. P. Van Duyne, *J. Electroanal. Chem.* **1977**, *84*, 1.
[3] M. G. Albrecht, J. A. Creighton, *J. Am. Chem. Soc.* **1977**, *99*, 5215.
[4] S.-Y. Ding, J. Yi, J.-F. Li, B. Ren, D.-Y. Wu, R. Panneerselvam, Z.-Q. Tian, *Nat. Rev. Mater.* **2016**, *1*, 16021.
[5] S. S. R. Dasary, A. K. Singh, D. Senapati, H. Yu, P. C. Ray, *J. Am. Chem. Soc.* **2009**, *131*, 13806.
[6] W. E. Doering, S. M. Nie, *J. Phys. Chem. B* **2002**, *106*, 311.
[7] H. X. Xu, J. Aizpurua, M. Kall, P. Apell, *Phys. Rev. E* **2000**, *62*, 4318.
[8] J. P. Camden, J. A. Dieringer, J. Zhao, R. P. Van Duyne, *Accounts. Chem. Res.* **2008**, *41*, 1653.
[9] D.-Y. Wu, J.-F. Li, B. Ren, Z.-Q. Tian, *Chem. Soc. Rev.* **2008**, *37*, 1025.
[10] J. R. Lombardi, R. L. Birke, *J. Phys. Chem. C* **2008**, *112*, 5605.
[11] J. R. Lombardi, R. L. Birke, *Accounts. Chem. Res.* **2009**, *42*, 734.
[12] J. Kim, Y. Jang, N.-J. Kim, H. Kim, G.-C. Yi, Y. Shin, M. H. Kim, S. Yoon, *Front. Chem.* **2019**, *7*, 00582.
[13] M. J. Seo, G. W. Kim, P. V. Tsalu, S. W. Moon, J. W. Ha, *Nanoscale Horiz.* **2020**, *5*, 345.
[14] Y. Yang, J. Li, M. Zhang, P. Song, X. Lu, Y. Ding, *J. Raman. Spectrosc.* **2021**, *52*, 1275.
[15] M. Fan, G. F. S. Andrade, A. G. Brolo, *Anal. Chim. Acta* **2020**, *1097*, 1.
[16] R. Liu, S. Li, J.-F. Liu, *TRAC-Trend. Anal. Chem.* **2017**, *97*, 188.
[17] F. Wanli, G. Weixing, J. Jian, W. Dongmei, F. Meikun, *Luminescence* **2021**, *37*, 82.
[18] L. Yanghe, W. Xiaoliang, L. Qingye, L. Aihui, H. Xingcun, J. Zhiliang, *Luminescence* **2017**, *33*, 131.
[19] C. Serafinelli, A. Fantoni, E. C. B. A. Alegria, M. Vieira, *Biosensors-Basel* **2022**, *12*, 225.
[20] Z. Zeng, Y. Liu, J. Wei, *TRAC-Trend. Anal. Chem.* **2016**, *75*, 162.
[21] S. Ji, G. Lin, W. Wenjun, G. Zhengjun, W. Dongmei, F. Meikun, *Luminescence* **2020**, *35*, 808.
[22] M. Jia, S. Li, L. Zang, X. Lu, H. Zhang, *Nanomaterials* **2018**, *8*, 730.
[23] L. Li, X.-y. He, S.-f. Li, C. Ge, Y. Xu, *Spectrosc. Spect. Anal* **2021**, *41*, 1661.
[24] J. Sun, L. Gong, W. Wang, Z. Gong, D. Wang, M. Fan, *Luminescence* **2020**, *35*, 808.
[25] P. Ma, F. Liang, Y. Sun, Y. Jin, Y. Chen, X. Wang, H. Zhang, D. Gao, D. Song, *Microchim. Acta* **2013**, *180*, 1173.
[26] W. Wang, B. Zhang, Y. Zhang, P. Ma, X. Wang, Y. Sun, D. Song, Q. Fei, *Spectrochim. Acta a* **2021**, *261*, 120057.
[27] L. Luo, Y. Chen, L. Zhang, Y. Li, H. Li, H. Zhang, Y. Tian, *Microchim. Acta* **2017**, *184*, 595.
[28] P. C. Lee, D. Meisel, *J. Phys. Chem.* **1982**, *86*, 3391.
[29] P. C. Lee, D. Meisel, *Chem. Phys. Lett.* **1983**, *99*, 262.
[30] M. V. Canamares, J. V. Garcia-Ramos, J. D. Gomez-Varga, C. Domingo, S. Sanchez-Cortes, *Langmuir* **2005**, *21*, 8546.
[31] U. Nickel, A. Z. Castell, K. Poppl, S. Schneider, *Langmuir* **2000**, *16*, 9087.
[32] J. Turkevich, P. C. Stevenson, J. Hillier, *Discuss. Faraday Soc.* **1951**, *11*, 55.
[33] G. Frens, *Nature* **1973**, *241*, 20.
[34] N. Leopold, B. Lendl, *J. Phys. Chem. B* **2003**, *107*, 5723.
[35] A.-S. Tatar, C. Farcau, A. Vulpoi, S. Boca, S. Astilean, *Spectrochim. Acta, Part a* **2022**, *273*, 121069.
[36] Q.-Y. Jiang, D. Li, Y. Liu, Z.-S. Mao, Y. Yu, P. Zhu, Q. Xu, Y. Sun, L. Hu, J. Wang, J. Chen, F. Chen, Y. Cao, *Sensor Actuat. B-Chem* **2021**, *344*, 130290.
[37] G. Kumar, R. K. Soni, *Plasmonics* **2021**, *17*, 559.
[38] H. Guo, F. Ruan, L. Lu, J. Hu, J. Pan, Z. Yang, B. Ren, *J. Phys. Chem. C* **2009**, *113*, 10459.
[39] H.-L. Wu, C.-H. Kuo, M. H. Huang, *Langmuir* **2010**, *26*, 12307.
[40] K. J. Si, P. Guo, Q. Shi, W. Cheng, *Anal. Chem.* **2015**, *87*, 5263.
[41] H. Yuan, C. G. Khoury, H. Hwang, C. M. Wilson, G. A. Grant, V.-D. Tuan, *Nanotechnology* **2012**, *23*, 075102.
[42] J. Xie, Q. Zhang, J. Y. Lee, D. I. C. Wang, *ACS Nano* **2008**, *2*, 2473.
[43] J. Yang, G. Song, L. Zhou, X. Wang, L. You, J. Li, *Appl. Surf. Sci.* **2021**, *539*, 147744.
[44] M. Sun, P. Chen, A. Zhao, F. Zuo, *Anal. Methods* **1923**, *2019*, 11.
[45] A. Gopinath, S. V. Boriskina, W. R. Premasiri, L. Ziegler, B. M. Reinhard, L. Dal Negro, *Nano Lett.* **2009**, *9*, 3922.
[46] H. Liu, Z. Yang, L. Meng, Y. Sun, J. Wang, L. Yang, J. Liu, Z. Tian, *J. Am. Chem. Soc.* **2014**, *136*, 5332.

[47] Y. Kalachyova, M. Erzina, P. Postnikov, V. Svorcik, O. Lyutakov, *Appl. Surf. Sci.* **2018**, *458*, 95.
[48] K. Xu, R. Zhou, K. Takei, M. Hong, *Adv. Sci.* **2019**, *6*, 1900925.
[49] Y. Yang, X. Ling, W. Qiu, J. Bian, X. Zhang, Q. Chen, *J. Phys. Chem. C* **2022**, *126*, 10722.
[50] C.-C. Huang, C.-Y. Cheng, Y.-S. Lai, *Trends Food Sci. Tech.* **2020**, *100*, 349.
[51] X. Liu, J. Ma, P. Jiang, J. Shen, R. Wang, Y. Wang, G. Tu, *ACS Appl. Mater. Inter.* **2020**, *12*, 45332.
[52] J. Luo, Z. Wang, Y. Li, C. Wang, J. Sun, W. Ye, X. Wang, B. Shao, *Sensor Actuat. B-Chem* **2021**, *347*, 347.
[53] M. Zhang, J. Pan, X. Xu, G. Fu, L. Zhang, P. Sun, X. Yan, F. Liu, C. Wang, X. Liu, G. Lu, *Anal. Chem.* **2022**, *94*, 4850.
[54] S. Kim, J.-H. Joo, W. Kim, A. Bang, H. W. Choi, S. W. Moon, S. Choi, *Sensor Actuat. B-Chem* **2021**, *343*, 130102.
[55] F. Zeng, T. Mou, C. Zhang, X. Huang, B. Wang, X. Ma, J. Guo, *Analyst* **2019**, *144*, 137.
[56] H. Cheng, L. Yi, J. Wu, G. Li, G. Zhao, Z. Xiao, B. Hu, L. Zhao, J. Tian, *Biosens. Bioelectron.* **2021**, *189*, 113266.
[57] H. Yuan, W. Ji, S. Chu, Q. Liu, S. Qian, J. Guang, J. Wang, X. Han, J.-F. Masson, W. Peng, *ACS Sens.* **2019**, *4*, 704.
[58] P. Ma, F. Liang, Q. Yang, D. Wang, Y. Sun, X. Wang, D. Gao, D. Song, *Microchim. Acta* **2014**, *181*, 975.
[59] P. Ma, F. Liang, Q. Diao, D. Wang, Q. Yang, D. Gao, D. Song, X. Wang, *RSC Adv.* **2015**, *5*, 32168.
[60] L. Chongning, W. Xiaoliang, L. Aihui, L. Yanghe, W. Guiqing, J. Zhiliang, *Luminescence* **2018**, *33*, 1113.
[61] W. Liao, Y. Chen, L. Huang, Y. Wang, Y. Zhou, Q. Tang, Z. Chen, K. Liu, *Microchim. Acta* **2021**, *188*, 354.
[62] Y. Zhao, B.-y. Wen, Y.-w. Huang, H. Zhang, J.-n. Lu, J.-f. Li, *Spectrosc. Spect. Anal* **2018**, *38*, 3769.
[63] X. Bu, Z. Zhang, L. Zhang, P. Li, J. Wu, H. Zhang, Y. Tian, *Sensor Actuat. B-Chem* **2018**, *273*, 1519.
[64] C. Wang, M. Shang, H. Wei, M. Zhang, W. Zou, X. Meng, W. Chen, H. Shao, Y. Lai, *Sensor Actuat. B-Chem* **2021**, *346*, 130594.
[65] G. Brackx, D. Guinoiseau, L. Duponchel, A. Gelabert, V. Reichel, S. Zrig, J.-M. Di Meglio, M. F. Benedetti, J. Gaillardet, G. Charron, *Sci. Rep.* **2020**, *10*, 1883.
[66] H. Ge, R. Yin, P. Su, L. Yu, M. Lei, M. Sun, Z. Sun, S. Wang, *Microchim. Acta* **2022**, *189*, 44.
[67] D. K. Sarfo, E. L. Izake, A. P. O'Mullane, G. A. Ayoko, *Sensor Actuat. B-Chem* **2018**, *255*, 1945.
[68] S. Zou, L. Ma, J. Li, Z. Xie, D. Zhao, Y. Ling, Z. Zhang, *Talanta* **2018**, *186*, 452.
[69] L. Zhang, J. Liu, G. Zhou, Z. Zhang, *Nanomaterials* **2020**, *10*, 826.
[70] B. Chandu, M. S. S. Bharati, P. Albrycht, S. V. Rao, *Opt. Laser Technol.* **2020**, *131*, 106454.
[71] J. D. Weatherston, S. Yuan, C. V. Mashuga, H.-J. Wu, *Sensor Actuat. B-Chem* **2019**, *297*, 126765.
[72] D. Zhang, L. Peng, X. Shang, W. Zheng, H. You, T. Xu, B. Ma, B. Ren, J. Fang, *Nat. Commun.* **2020**, *11*, 2603.
[73] B. Zhou, M. Mao, X. Cao, M. Ge, X. Tang, S. Li, D. Lin, L. Yang, J. Liu, *Anal. Chem.* **2018**, *90*, 3826.
[74] S. Lin, W. Hasi, X. Lin, S. Han, T. Xiang, S. Liang, L. Wang, *ACS Sens.* **2020**, *5*, 1465.
[75] Q. Wang, Z. Shi, Z. Wang, Y. Zhao, J. Li, H. Hu, Y. Bai, Z. Xu, H. Zhangsun, L. Wang, *Anal. Chim. Acta* **2020**, *1129*, 126.
[76] H. S. Jung, E. H. Koh, C. Mun, J. Min, W. Sohng, H. Chung, J.-Y. Yang, S. Lee, H. J. Kim, S.-G. Park, M.-Y. Lee, D.-H. Kim, *J. Mater. Chem. C* **2019**, *7*, 13059.
[77] M. Zhang, Y. Liu, P. Jia, Y. Feng, S. Fu, J. Yang, L. Xiong, F. Su, Y. Wu, Y. Huang, *ACS Appl. Nano Mater.* **2021**, *4*, 1019.
[78] X.-J. Li, Y.-T. Li, H.-X. Gu, P.-F. Xue, L.-X. Qin, S. Han, *Anal. Methods* **2022**, *14*, 781.
[79] Y.-Y. Yang, Y.-T. Li, X.-J. Li, L. Zhang, E. K. Fodjo, S. Han, *Chem. Eng. J.* **2020**, *402*, 125179.
[80] P. Ma, F. Liang, D. Wang, Q. Yang, B. Cao, D. Song, D. Gao, X. Wang, *Microchim. Acta* **2015**, *182*, 167.
[81] X. Guo, Y. Wu, Y. Ying, Y. Wen, F. Wang, Q. Ke, H. Yang, *J. Raman. Spectrosc.* **2018**, *49*, 215.
[82] P. Li, P. Li, X. Tan, J. Wang, Y. Zhang, H. Han, L. Yang, *Anal. Bioanal. Chem.* **2020**, *412*, 2863.
[83] Z. Qing, Y. Lingling, M. Lu, Y. Wenqing, L. Tingsheng, L. Aihui, J. Zhiliang, *Luminescence* **2014**, *30*, 303.
[84] M. Liszewska, B. Bartosewicz, B. Budner, B. Nasilowska, M. Szala, J. L. Weyher, I. Dziecielewski, Z. Mierczyk, B. J. Jankiewicz, *Vib. Spectrosc.* **2019**, *100*, 79.
[85] M. S. S. Bharati, C. B. Venugopal, V. R. Soma, *Front. Phys.* **2018**, *6*, 00028.
[86] K. Milligan, N. C. Shand, D. Graham, K. Faulds, *Anal. Chem.* **2020**, *92*, 3253.
[87] R. Gao, D. Li, Q. Zhang, S. Zheng, X. Ren, W. Deng, *Sensor Actuat. B-Chem* **2021**, *328*, 128960.
[88] K. J. Squire, K. Sivashanmugan, B. Zhang, J. Kraai, G. Rorrer, A. X. Wang, *ACS Appl. Nano Mater.* **2020**, *3*, 1656.
[89] M. Lafuente, D. Sanz, M. Urbiztondo, J. Santamaria, M. Pilar Pina, R. Mallada, *J. Hazard. Mater.* **2020**, *384*, 121279.
[90] F. Zeng, W. Duan, B. Zhu, T. Mu, L. Zhu, J. Guo, X. Ma, *Anal. Chem.* **2019**, *91*, 1064.
[91] G. Palermo, M. Rippa, Y. Conti, A. Vestri, R. Castagna, G. Fusco, E. Suffredini, J. Zhou, J. Zyss, A. De Luca, L. Petti, *ACS Appl. Mater. Inter.* **2021**, *13*, 43715.
[92] D. Li, D. Y. Lv, Q. X. Zhu, H. Li, H. Chen, M. M. Wu, Y. F. Chai, F. Lu, *Food Chem.* **2017**, *224*, 382.
[93] P. Zhang, L. Wang, X. Wei, T. Lin, H. Wang, X. Liu, D. Zheng, *J. Appl. Spectrosc.* **2018**, *85*, 880.
[94] L. Tognaccini, M. Ricci, C. Gellini, A. Feis, G. Smulevich, M. Becucci, *Molecules* **2019**, *24*, 292.
[95] N. Creedon, P. Lovera, J. G. Moreno, M. Nolan, A. O'Riordan, *J. Phys. Chem. A* **2020**, *124*, 7238.
[96] C. Yao, F. Cheng, C. Wang, Y. Wang, X. Guo, Z. Gong, M. Fan, Z. Zhang, *Anal. Methods* **2013**, *5*, 5560.
[97] Q. Xu, X. Guo, L. Xu, Y. Ying, Y. Wu, Y. Wen, H. Yang, *Sensor Actuat. B-Chem* **2017**, *241*, 1008.
[98] X. Gong, M. Tang, Z. Gong, Z. Qiu, D. Wang, M. Fan, *Food Chem.* **2019**, *295*, 254.
[99] M. Qiao, S. Liu, Z. Liu, J. Yang, J. Zhu, X. Hu, *Food Anal. Methods* **2014**, *7*, 1737.
[100] S. W. Kim, J. R. Liu, *J. Plant Biol.* **2009**, *52*, 625.
[101] D. Wang, F. Liang, P. Ma, Q. Yang, D. Gao, D. Song, X. Wang, *Food Anal. Methods* **2016**, *9*, 934.
[102] H. Wu, Y. Luo, C. Hou, D. Huo, W. Wang, J. Zhao, Y. Lei, *Talanta* **2019**, *200*, 84.
[103] H. Wu, Y. Luo, C. Hou, D. Huo, Y. Zhou, S. Zou, J. Zhao, Y. Lei, *Sensor Actuat. B-Chem* **2019**, *285*, 123.
[104] O. Guselnikova, P. Postnikov, R. Elashnikov, E. Miliutina, V. Svorcik, O. Lyutakov, *Anal. Chim. Acta* **2019**, *1068*, 70.
[105] Y.-L. Chang, I. C. Lai, L.-C. Lu, S.-W. Chang, A. Y. Sun, D. Wan, H.-L. Chen, *Biosens. Bioelectron.* **2022**, *200*, 113920.
[106] L. Zhang, Y. Guo, R. Hao, Y. Shi, H. You, H. Nan, Y. Dai, D. Liu, D. Lei, J. Fang, *Nat. Commun.* **2021**, *12*, 6849.
[107] S. Wang, H. Wang, T. Du, T. Bu, J. Xu, S. Liu, X. Yin, Y. Wang, D. Zhang, J. Sun, J. Wang, *Food Chem.* **2022**, *393*, 133351.
[108] L. Hou, Y. Ji, J. Zhao, L. Zhao, *Microchem. J.* **2022**, *179*, 107664.
[109] J. Du, Z. An, Y. Hu, X. Yi, H. Zhou, J. Zhan, M. Wu, *J. Environ. Sci.* **2022**, *122*, 227.
[110] S. Schwarz, C. Kehrenberg, T. R. Walsh, *Int. J. Antimicrob. Ag.* **2001**, *17*, 431.

[111] Q. Shi, J. Huang, Y. Sun, R. Deng, M. Teng, Q. Li, Y. Yang, X. Hu, Z. Zhang, G. Zhang, *Microchim. Acta* **2018**, *185*, 84.
[112] V. Moreno, A. Adnane, R. Salghi, M. Zougagh, A. Ríos, *Talanta* **2019**, *194*, 357.
[113] Z. Ao, F. Jijun, Y. Jingci, H. Mengyun, Z. Ling, Z. Heping, *Appl. Surf. Sci.* **2022**, *583*, 152543.
[114] Q. Yang, F. Liang, D. Wang, P. Ma, D. Gao, J. Han, Y. Li, A. Yu, D. Song, X. Wang, *Anal. Methods* **2014**, *6*, 8388.
[115] K. Ge, Y. Hu, Y. Zheng, P. Jiang, G. Li, *Talanta* **2021**, *235*, 122743.
[116] S. Guangyun, L. Chongning, W. Guiqing, Z. Xinghui, L. Aihui, J. Zhiliang, *Luminescence* **2015**, *31*, 640.
[117] Y. Xiang, M. Li, X. Guo, Y. Wu, Y. Ying, Y. Wen, H. Yang, *Sensor Actuat. B-Chem* **2018**, *262*, 44.
[118] D. Zhang, H. You, L. Yuan, R. Hao, T. Li, J. Fang, *Anal. Chem.* **2019**, *91*, 4687.
[119] Y. Yang, G. Li, P. Wang, L. Fan, Y. Shi, *Talanta* **2022**, *243*, 123369.
[120] C. Pan, B. Zhu, C. Yu, *Biosensors-Basel* **2020**, *10*, 200.
[121] S. C. Pinzaru, C. Muller, I. Ujevic, M. M. Venter, V. Chis, B. Glamuzina, *Talanta* **2018**, *187*, 47.
[122] L.-L. Qu, Q. Jia, C. Liu, W. Wang, L. Duan, G. Yang, C.-Q. Han, H. Li, *J. Chromatogr. A* **2018**, *1579*, 115.
[123] B. b. Zhang, Y. Shi, H. Chen, Q. x. Zhu, F. Lu, Y. w. Li, *Anal. Chim. Acta* **2018**, *997*, 35.
[124] R. Alder, J. Hong, E. Chow, J. Fang, F. Isa, B. Ashford, C. Comte, A. Bendavid, L. Xiao, K. Ostrikov, S. Fu, A. B. Murphy, *Sensors* **2021**, *21*, 810.
[125] H. Wang, Z. Xue, Y. Wu, J. Gilmore, L. Wang, L. Fabris, *Anal. Chem.* **2021**, *93*, 9373.
[126] S. Weng, R. Dong, Z. Zhu, D. Zhang, J. Zhao, L. Huang, D. Liang, *Spectrochim. Acta a* **2018**, *189*, 1.
[127] M. Mao, B. Zhou, X. Tang, C. Chen, M. Ge, P. Li, X. Huang, L. Yang, J. Liu, *Chem. – Eur. J.* **2018**, *24*, 4094.
[128] E. C. Tackman, M. J. Trujillo, T.-L. E. Lockwood, G. Merga, M. Lieberman, J. P. Camden, *Anal. Methods* **2018**, *10*, 4718.
[129] B. Hao, J. Wu, Y. Ding, L. Zhang, B. Zhao, Y. Tian, *Anal. Bioanal. Chem.* **2020**, *412*, 7827.
[130] P.-C. Yang, P.-H. Lin, C.-C. Huang, T. Wu, Y.-W. Lin, *Microchem. J.* **2020**, *157*, 104983.
[131] P. Wu, L.-B. Zhong, Q. Liu, X. Zhou, Y.-M. Zheng, *Nanoscale* **2019**, *11*, 12829.
[132] N. Lyu, V. K. Rajendran, R. J. Diefenbach, K. Charles, S. J. Clarke, A. Engel, H. Rizos, M. P. Molloy, Y. Wang, I. Sydney Colorectal Cancer Study, *Nanotheranostics* **2020**, *4*, 224.
[133] C. Dallari, C. Credi, E. Lenci, A. Trabocchi, R. Cicchi, F. S. Pavone, *J. Phys.-Photon.* **2020**, *2*, 4008.
[134] Y. Li, X. Liu, J. Guo, Y. Zhang, J. Guo, X. Wu, B. Wang, X. Ma, *Nanomaterials* **2021**, *11*, 1496.
[135] C. Hu, F. Peng, F. Mi, Y. Wang, P. Geng, L. Pang, Y. Ma, G. Li, Y. Li, M. Guan, *Anal. Chim. Acta* **2022**, *1191*, 339289.
[136] T.-J. Li, B.-Y. Wen, X.-H. Ma, W.-T. Huang, J.-Z. Wu, X.-M. Lin, Y.-J. Zhang, J.-F. Li, *Anal. Chem.* **2021**, 94.
[137] M. Lu, W. Guiqing, Y. Lingling, L. Zujun, L. Yanghe, L. Aihui, J. Zhiliang, *Luminescence* **2014**, *30*, 790.
[138] W. Zhu, B.-Y. Wen, L.-J. Jie, X.-D. Tian, Z.-L. Yang, P. M. Radjenovic, S.-Y. Luo, Z.-Q. Tian, J.-F. Li, *Biosens. Bioelectron.* **2020**, *154*, 112067.
[139] Y. Bu, G. Zhu, S. Li, R. Qi, G. Bhave, D. Zhang, R. Han, D. Sun, X. Liu, Z. Hu, X. Liu, *ACS Appl. Nano Mater.* **2018**, *1*, 410.
[140] H. T. Ngo, E. Freedman, R. A. Odion, P. Strobbia, A. S. D. S. Indrasekara, P. Vohra, S. M. Taylor, T. Vo-Dinh, *Sci. Rep.* **2018**, *8*, 4075.
[141] W. Wang, Y. Li, A. Nie, G.-C. Fan, H. Han, *Analyst* **2021**, *146*, 848.
[142] S.-W. Hu, S. Qiao, J.-B. Pan, B. Kang, J.-J. Xu, H.-Y. Chen, *Talanta* **2018**, *179*, 9.
[143] D. Zhang, L. Huang, B. Liu, Q. Ge, J. Dong, X. Zhao, *Microchim. Acta* **2019**, *186*, 699.
[144] W. Wang, D. Li, Y. Zhang, W. Zhang, P. Ma, X. Wang, D. Song, Y. Sun, *Microchim. Acta* **2020**, *187*, 604.
[145] W. Wang, Y. Zhang, W. Zhang, Y. Liu, P. Ma, X. Wang, Y. Sun, D. Song, *Anal. Chim. Acta* **2021**, *1183*, 338989.
[146] T. Vi, B. Walkenfort, M. Koenig, M. Salehi, S. Schluecker, *Angew. Chem. Int. Edit.* **2019**, *58*, 442.
[147] Y.-F. Tian, C.-F. Ning, F. He, B.-C. Yin, B.-C. Ye, *Analyst* **2018**, *143*, 4915.
[148] Z. Huang, S. Siddhanta, G. Zheng, T. Kickler, I. Barman, *Angew. Chem. Int. Edit.* **2020**, *59*, 5972.
[149] Y. Zhu, J. Wu, K. Wang, H. Xu, M. Qu, Z. Gao, L. Guo, J. Xie, *Talanta* **2021**, *224*, 121852.
[150] W. Zhang, L. Jiang, R. J. Diefenbach, D. H. Campbell, B. J. Walsh, N. H. Packer, Y. Wang, *ACS Sens.* **2020**, *5*, 764.
[151] H. Liu, E. Dai, R. Xiao, Z. Zhou, M. Zhang, Z. Bai, Y. Shao, K. Qi, J. Tu, C. Wang, S. Wang, *Sensor Actuat. B-Chem* **2021**, *329*, 12916.
[152] H. Cha, H. Kim, Y. Joung, H. Kang, J. Moon, H. Jang, S. Park, H.-J. Kwon, I.-C. Lee, S. Kim, D. Yong, S.-W. Yoon, S.-G. Park, K. Guk, E.-K. Lim, H. G. Park, J. Choo, J. Jung, T. Kang, *Biosens. Bioelectron.* **2022**, *202*, 114008.
[153] D. Zhang, X. Zhang, R. Ma, S. Deng, X. Wang, X. Wang, X. Zhang, X. Huang, Y. Liu, G. Li, J. Qu, Y. Zhu, J. Li, *Water Res.* **2021**, *200*, 117243.
[154] M. Xiao, K. Xie, X. Dong, L. Wang, C. Huang, F. Xu, W. Xiao, M. Jin, B. Huang, Y. Tang, *Anal. Chim. Acta* **2019**, *1053*, 139.
[155] S. Kim, S. H. Lee, Y. J. Kim, H. J. Lee, S. Choi, *Anal. Methods* **2019**, *11*, 5381.
[156] M. L. Shaine, W. R. Premasiri, H. M. Ingraham, R. Andino, P. Lemler, A. N. Brodeur, L. D. Ziegler, *Analyst* **2020**, *145*, 6097.
[157] E. Thayer, W. Turner, S. Blama, M. S. Devadas, E. M. Hondrogiannis, *MRS Commun.* **2019**, *9*, 948.
[158] Y. He, M. Wen, X. Zhou, F. Gao, H. Lu, *Anal. Lett.* **2022**, *55*, 555.

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