Review

Summarizing Advanced Progress in Nanostructure-Sensitized Surface-Enhanced Raman Sensing Toward Food Safety

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Posted Date: 27 January 2025

doi: 10.20944/preprints202501.1938.v1

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Summarizing Advanced Progress in Nanostructure-Sensitized Surface-Enhanced Raman Sensing toward Food Safety

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Abstract: Food safety is directly related to human health and has attracted intense attention all over the world. Surface-enhanced Raman scattering (SERS), as a rapid and selective technique, has been widely applied in monitoring food safety. SERS substrates, as an essential factor for sensing design, greatly influence the analytical performance. Currently, nanostructure-based SERS substrates have garnered significant interest due to their excellent merits in improving the sensitivity, specificity, and stability, holding great potential for rapid and accurate sensing toward food contaminants in complex matrices. This review summarizes the fundamentals of Raman spectroscopy and the used nanostructures for designing SERS platform, including precious metal nanoparticles, metal-organic frameworks, polymers, and semiconductors. Moreover, it introduces the mechanisms and applications of nanostructures in enhancing SERS signals for monitoring hazardous substances, such as foodborne bacteria, pesticide and veterinary drug residues, food additives, illegal adulterants, and packaging material contamination. Finally, the review offers broad prospects in sustainable, environmentally friendly, and large-scale analysis to evaluate food safety.

Keywords: Surface-enhanced Raman scatter; nanostructures; sensing platform; chemical mechanism; food safety; hazardous substances

1. Introduction

Food safety is a critical issue in the global public health domain, directly impacting consumer health[1–3]. With the increasing complexity of modern food production and supply chains, the contamination of harmful substances in food has become more pronounced[4,5]. The harmful substances are mentioned as microorganisms[6–10], chemical substances[11–15], and physical contaminants[16–19] that may be introduced during food harvest, processing, storage, and sale[20–25]. As mentioned, microbiological contamination, such as bacteria[3,26–30], viruses[31–34], and fungi[35–38], can lead to outbreaks of foodborne diseases, posing significant challenges to public health safety[23,39,40]. Chemical contamination, including residues of veterinary drugs[39,41,42] and pesticides[43–46], heavy metals pollution[47–52], food additives[53–56] and illegal adulterants[57–59], is also an issue that cannot be overlooked in food safety. Long-term intake of these chemical substances may have chronic effects on human health, including carcinogenesis, neurological damage, and other health issues[60,61]. Physical contamination, such as glass, metal, rocks, fish bones[62], and packaging contamination[17,18], although not usually causing acute health risks, can cause physical injury and discomfort to consumers.

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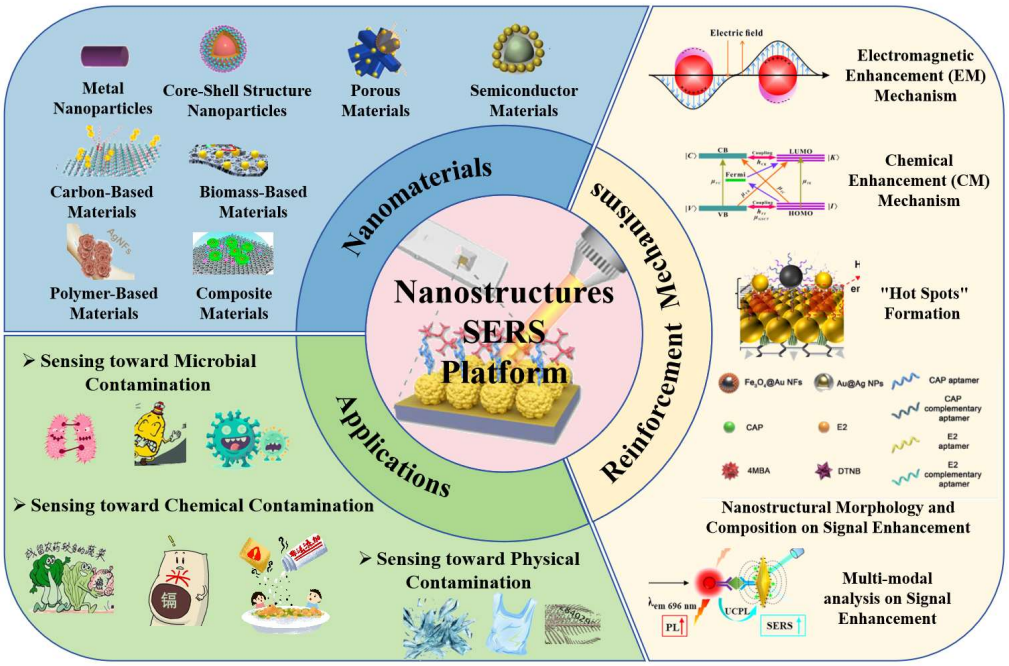

Scheme 1. Overview of Nanostructures as SERS Substrates: Nanomaterials, Reinforcement Mechanisms, and Applications in Food Hazard Detection.

To protect consumers from the potential hazards, governments and international organizations have established food safety standards[63–66]. Although the accuracy of traditional methods toward food safety assessment, they often have some limitations, such as high cost, long duration, laborious operation, and inability to achieve on-site analysis[67–70]. Therefore, the development of rapid and sensitive technologies is crucial for improving the efficiency of food safety management. Fortunately, Surface-enhanced Raman spectroscopy (SERS) has shown great potential in the field of food safety, which can provide detailed information on molecular vibrations of trace components in complex samples. [71–74]. SERS pattern, with its high sensitivity, rapid response, and molecular fingerprint characteristics, provides a powerful solution for detecting various harmful substances in food. Consequently, great efforts have been devoted to SERS development, aiming to promptly monitor microorganisms, chemical substances, and physical contaminants in assessing food safety risks.

To design a successful SERS strategy, the sensing platform is considered as a key foctor on analytical performance. In this respect, nanostructures, due to their unique physical and chemical properties[21,75–79], are very popular in SERS platform development for enhancing Raman signals. For example, metal nanostructures such as gold (Au) and silver (Ag) nanoparticles, have a localized surface plasmon resonance (LSPR) effect and can generate strong electromagnetic fields on sensing platform, greatly amplifying the Raman scattering signals of nearby molecules. With help of nanostructures, SERS platform has been applied in detecting mycotoxins[80–82], pesticide residues[45,83–86], and illegal additives[87,88] with high sensitivity for ensuring food safety, in which nanostructures not only amplify SERS signal but also serve as carriers and markers [89,90].

Herein, this review summarized the analytical mechanism of SERS patterns. Moreover, the enhancement behavior of nanostructures (e.g., metal-based, carbon-based nanostructures)toward Raman signals was explored for further improving the sensitivity of SERS platform. Benefitting from the merits of nanostructures, SERS mode was applied in monitoring food hazards, contributing to ensuring the efficiency of food safety.

2. Analytical Mechanism of SERS

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2.1. Basic Theory of SERS

As known, when a beam of light strikes an uneven substrate, the light can be reflected, scattered, or absorbed (Figure 1A). During the mentioned process, the scattered part undergoes a change in frequency, it is named as Raman scattering[91]; while the frequency remains unchanged, it is Rayleigh scattering. From a microscopic perspective, when an excited molecule absorbs the energy of a photon, it can transition to a virtual state, and then return to the ground state, resulting in Rayleigh scattering. Nevertheless, when the molecule reaches another energy level, it is called Raman scattering, in which it can be classified as anti-Stokes scattering (the molecule absorbs energy) and Stokes scattering (the molecule loses energy)[92]. The energy difference between two photons is given as Equation (1):

$$\Delta E = h\Delta v = \quad (v - v') \qquad (1)$$

where Δv represents the frequency shift in the Raman scattering spectrum.

Unlike typical Raman spectra, the intensity of SERS spectra is dependent on the interaction of rough metal surfaces (Ag or Au nanoparticles) with the target molecule[93]. Specifically, SERS has the following characteristics: (1) high sensitivity, with an intensity that is 7 to 14 orders of magnitude greater than that of spontaneous Raman scattering; (2) excellent selectivity, selective amplification of certain normal vibrations associated with a given electronic absorption band. With these merits, SERS offers an effective technique for studying the vibrational and electronic structures of chromophores within biomolecules or entire cells, and it can be applied in the fields of life sciences and food to investigate specific chromophores that play crucial roles in biological processes.

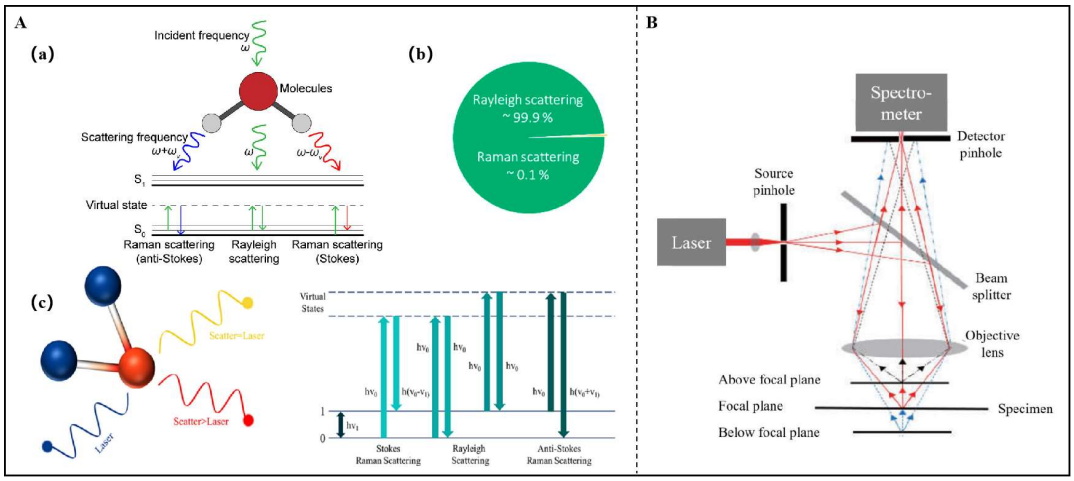

Figure 1. (A) Schematic diagram of (a) Raman scattering effect; (b) Photon scattering of Rayleigh scattering accounting for about 99.9% , Raman scatteringabout 0.1%; (c) Transition energy level of Stokes, anti-Stokes and Rayleigh scattering[91,94,95]. (B) Schematic setup of confocal Raman microscope[96].

2.2. Raman Signal Acquisition

Raman microscopy[96], which integrates Raman spectroscopy with an optical microscope, enables the acquisition of Raman scattering through an objective lens (Figure 1B). Meanwhile, confocal Raman microscopy directs a point light source through pinhole and beam splitter, focusing it to diffraction-limited spot on the specimen via objective lens. The scattered or emitted light is collected, collimated, and passed through detector pinhole before reaching a spectrometer. The detector pinhole serves as depth selector, rejecting out-of-focus light and selectively gathering signals from the focal plane. Especially, confocal microscopes have emerged as valuable analytical tools, offering superior depth resolution and enhanced image contrast through the suppression of stray light.

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Raman imaging could exhibit chemical composition by integrating spatial (x, y dimensions) and spectral (wavelength dimension) information from Raman spectroscopy. There are two primary Raman imaging methodologies: scanning and wide-field imaging. As for scanning imaging, often facilitated by confocal microscopy, is conducted as follows: (1) Point Scanning: This method collects Raman spectra at each spatial location sequentially. The sample is precisely moved across a high-precision stage, controlling both lateral and axial positions. It offers high spectral resolution and full spectral capture, but is time-intensive and susceptible to laser-induced sample damage[96]. (2) Line Scanning: Broadening the spatial range of each scan with a laser line, this technique gathers a line of spatial and spectral data per measurement. The sample is automated along a stage axis perpendicular to the laser line. Despite the reduced Raman signal intensity, line scanning maintains high spectral resolution and is more time-efficient than point scanning[96]. Regarding wide-field Raman imaging, the entire sample area is simultaneously illuminated, enabling the acquisition of spatial data in a single, non-contact scan. Among the developed wide-field imaging, area scanning involves the selection of a specific Raman scattering spectral slice for analysis[96]. While this approach offers speed, it is limited by the complexity of spectral data discrimination.

2.3. SERS Superiority

The primary constraint of traditional Raman spectroscopy is the inherently weak signal, with only about 1 in 10^6 to 10^8 photons being inelastically scattered. This limitation can impede the detection of molecules at low concentrations, thereby restricting its utility in food industry applications[97]. SERS overcomes the shortcomings by employing metal-based sensing platform , greatly amplifying the Raman signal of even single molecule by several orders of magnitude, typically from 10^7 to 10^{14}. Specially, the assay principle involves the interaction between rough metal surfaces and target molecules, in which the inelastic light scattering of the target molecules is enhanced[98]. The enhancement factor can reach up to 10^{14}, thereby enabling single-molecule detection in certain cases. The development of SERS has also promoted the advancement of various other spectroscopic techniques.

According to whether the molecule(e.g., 4-Mercaptobenzoic acid (4-MBA), 4-aminothiolphenol(4-ATP)) is labeled with Raman or not, SERS patterns are categorized into two main strategies: label-free (direct) and label-based (indirect) SERS (Figure 2A). As for the former, label-free SERS could trace the intrinsic fingerprint of the analyte through its direct interaction with the sensing substrate, possessing the merits of simplicity, rapidity, cost-effectiveness, and lack of interference from other components. As for the latter, label-based SERS exploits signal tags that consist of specific Raman reporter molecules for capturing analytes . This approach offers the benefits of multiplex analysis, enhanced sensitivity, and improved repeatability over the label-free pattern[96,99–101].

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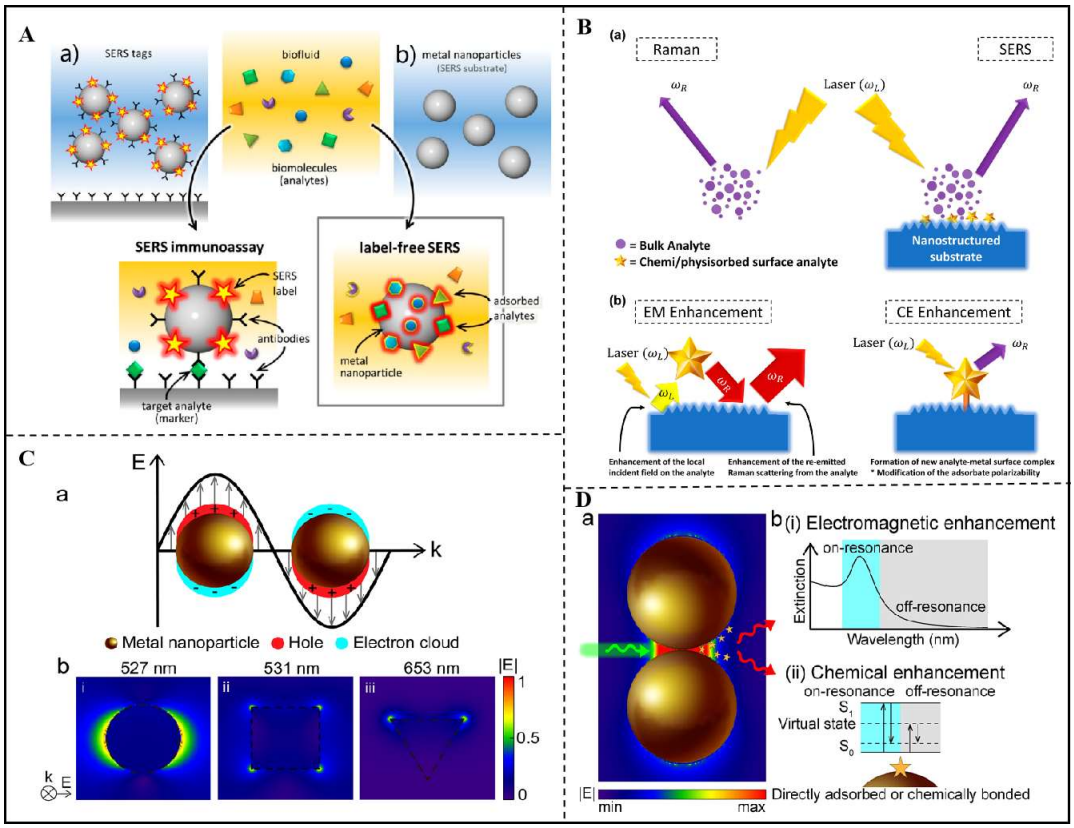

Figure 2. (A) (a) Indirect protocol. SERS tag with antibodies for selectively binding to the analyte , while Raman reporter for signal output. (b) Direct protocol. The analyte is adsorbed on the nanostructures and detected through its own Raman spectra[100]. (B) (a) Schematic comparison of the Raman and SERS phenomena. (b) SERS electromagnetic and chemical enhancements[91]. (C)LSPR on plasmonic nanostructures[95]. (a) Scheme of electron clouds oscillating opposite from the direction of electric field. (b) FDTD calculation of the on-resonance (wavelength labeled on the top of each figure) normalized electric field ($|E|$) distribution of (i) nanosphere, (ii) nanocube, and (iii) nanotriangle. (D) SERS effect[95]. (a) Scheme of electric field hot spot. (b) Two major enhancement mechanisms of SERS: (i) Electromagnetic enhancement: extinction spectrum showing the plasmonic on-resonance (cyan shaded) and off-resonance (gray shaded) wavelengths. (ii) Chemical enhancement: Jablonski diagram illustrating the enhancement from the molecular resonance (cyan) compared with the off-resonance situation (gray).

SERS enhancement is accomplished through two mechanisms (Figure 2B): electromagnetic (EM) and chemical enhancement (CM)[98]. The main point in the EM mechanism is to couple incident light with plasmonic nanostructures LSPRs such that the secondary electric field efficiently concentrates the EM field. When molecules are in close vicinity to plasmonic nanostructures, the amplified EM field enhances the SERS intensity (Figure 2C). The EM mechanism is considered to be the predominant contributor to SERS signal amplification with enhancement factor from 10^4 to 10^7. When molecules bind directly to plasmonic surface to form charge-transfer structure, CM is associated with the intrinsic chemical composition of the analyte, with enhancement factor usually in the order of 10 to 100[102]. With merits of wider range of excitation wavelengths, less photobleaching susceptibility, and the ability in multiplex assay, SERS is well qualified for tracing single molecule with Raman signal enhancement up to 10^{10}. As for SERS system, there are EM and CM enhancement (Figure 2D). The collective effects of EM and CM on SERS signal intensity (I_{SERS}) can be articulated as shown in Equation (2)[103,104].

$$I_{SERS} \propto EF_{EM} \times EF_{CM} \times N \times I_0 \quad (2)$$

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where I_0 is the incident light intensity, N is the number of Raman probe molecules irradiated on sensing substrate. As seen from the above formula, EF_{EM}, EF_{CM}, N, and I_0 were the key factors on SERS signal strength. When calculating the total EF, EF_{EM} and EF_{CM} are usually not separated, and EF value can be calculated according to the following equation:

$$EF = \frac{I_{SERS}/N_{SERS}}{I_{NOR}/N_{NOR}} \quad (3)$$

$$I_{SERS} = N_A S_{LAS} V C_{SERS}/S_{CON} \quad (4)$$

$$I_{NOR} = N_A S_{LAS} V C_{NOR}/S_{CON} \quad (5)$$

where N_{NOR} is molecule number in laser irradiation volume, N_{SERS} is total number of molecules adsorbed on sensing platform, N_A is Avogadro's constant, S_{LAS} represents the laser spot area. V is the volume of the solution, and S_{CON} is the contact area of the molecules, I_{SERS} indicates Raman signal strength of the molecule to be tested based on the enhanced substrate, I_{NOR} is Raman signal strength obtained from normal substrate. C_{SERS} is molecular concentration based on SERS substrate. C_{NOR} is based on the molecular concentration of normal substrate [103,104].

2.4. Spectral Statistics Characteristics

Raman spectral information is of vital importance for revealing subtle analyte details[105,106]. The related statistical analysis involves preprocessing Raman data to isolate diagnostic bands, constructing classification or predictive models, and subsequently deploying the models for analyte determination. Remarkably, data preprocessing is essential for eliminating spectral noise, artifacts, and irrelevant signals arising from environmental factors and instrumental imperfections[72,92,107]. The used techniques include spike removal, wavenumber calibration, intensity normalization, smoothing, background subtraction, normalization, and dimensionality reduction.

Chemometric analysis of Raman spectra facilitates the extraction of distinct information for sample classification and differentiation. According to the availability of prior knowledge, the models are categorized into unsupervised and supervised pattern recognition . In both, unsupervised pattern recognition, such as principal component analysis (PCA), uncovers underlying structures within unlabeled data and is often paired with clustering algorithms for sample classification. Supervised pattern recognition constructs a mathematical model based on a dataset of known categories, enabling the classification of unknown samples. Popular discriminant methods consist of linear discriminant, partial least squares discrimination, support vector machines (SVM), and artificial neural networks[108].

Additionally, predictive models ascertain the relationship of variables to forecast parameters of new observations. The selection of appropriate mathematical model is critical, and consequently, various evaluation metrics have been developed to refine model parameters and assess performance. For example, the determination coefficient (R^2) and root mean square error (RMSE) are used in optimizing model accuracy and reliability. Figure 3 summarizes some best practices for spectral statistics characteristics in SERS at various stages of experiments.

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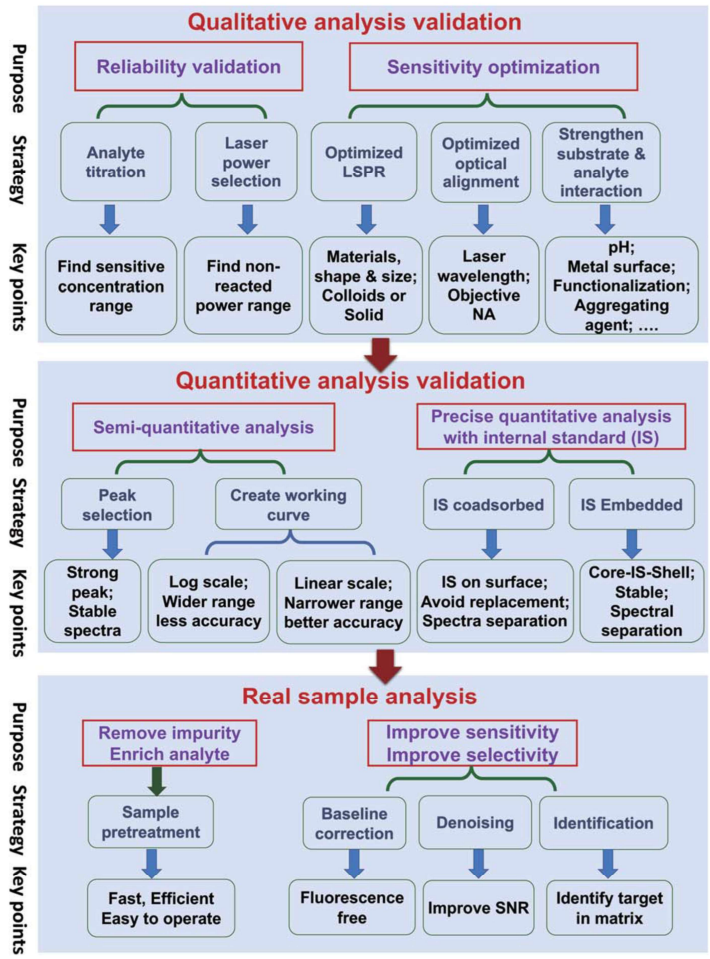

Figure 3. Steps for best practices for quantitative and qualitative detection using SERS to overcome the challenges at each stage with a goal of real-world applications[92].

3. Sensitizing Effect of Nanostructures Toward SERS Assay

With the rapid development of nanotechnology, the nanostructures have been endowed with outstanding magnetic, electrical, optical, mechanical, and catalytic properties[109–114] and consequently, have attracted enormous attention to SERS strategy for signal enhancement[115,116].

3.1. Classification and Preparation of Nanostructures in SERS

3.1.1. Classification of Nanostructures for Enhancing SERS Signals

The performance of SERS substrates is dependent on their ability for Raman signal enhancement. Fortunately, nanostructures could meet the demand for performance improvement of SERS analysisdue to their unique optical properties. As shown in Table 1 and Figure 4, the used nanostructures in SERS strategy comprise the following categories[117–119].

Table 1. Commonly used nanostructures in SERS platform.

Classification	Specific Materials	Characteristics
Metal Nanostructures[7,120]	Au, Ag, Metal Alloy	Widely used in SERS substrates due to their excellent LSPR property.

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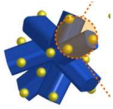
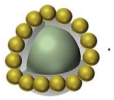
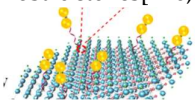
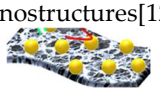
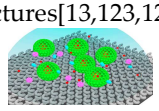
Core-Shell Structure [13,121,122] 	Au@Ag, Ag@Au	Optimizing SERS signals by adjusting the properties of the outer layer metal.
Porous Materials[39,123,124] 	Porous carbon (PC), Porous silicon (PS), Metal-organic frameworks (MOFs)	High specific surface area and good molecular sieving effects, effectively adsorbing target molecules and enhancing SERS signals.
Semiconductor Nanostructures[13,125] 	Titanium dioxide (TiO_2), Zinc oxide (ZnO)	Weak in SERS activity on their own, but can enhance signal strength when combined with metal nanoparticles.
Carbon-Based Nanostructures[126,127] 	Graphene and its derivatives (e.g., reduced graphene oxide)	Excellent conductivity and large specific surface area, effectively enhancing SERS signals.
Polymer-Based Nanostructures[128] 	Functionalized polymers (e.g., PMMA, PDMS)	Combining with metal nanoparticles to form composition for enhancing SERS signals.
Biomass-Based Nanostructures[129] 	Natural polymers (e.g., chitosan, gelatin)	Biocompatibility and tunability allow them to combine with metal nanoparticles for enhancing signals.
Composite Nanostructures[13,123,124,130,131] 	Combination of different nanostructures (e.g., metals with semiconductors, metals with porous materials)	Achieving synergistic effects to further enhance SERS signals.

As confirmed, the used nanostructures significantly enhance the intensity and sensitivity of SERS signals by providing abundant "hot spot" areas, increasing the adsorption of target molecules, and adjusting surface plasmon resonance behavior[132–134].

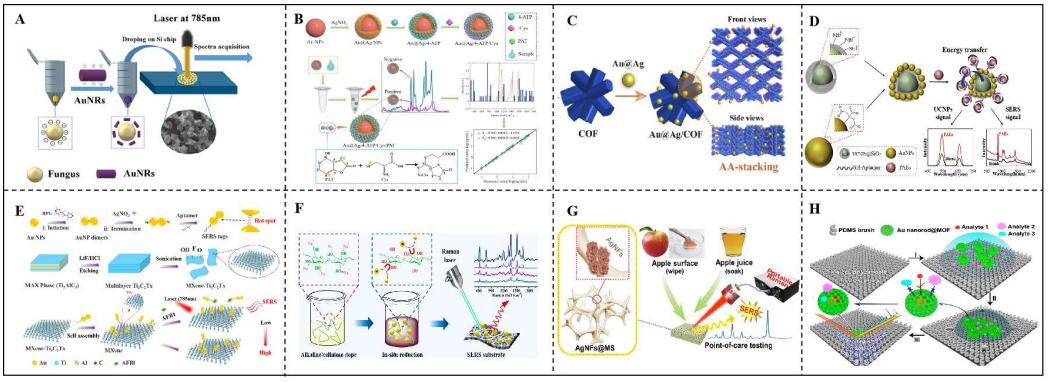


Figure 4. (A) Schematic illustration of SERS measurements using gold nanorods[7]. (B) Schematic diagram of SERS toward patulin based on NAR-SERS substrate (Au@Ag/4-ATP/Cys)[122]. (C) Schematic illustration of the

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synthesis of Au@Ag/COF SERS substrate[123]. (D) Schematic illustration of fluorescence and SERS bimodal nanosensor for Phthalate acid esters[13]. (E) Schematic illustration of SERS aptasensor based on AuNP dimers/MXenes assemblies [127]. (F) One-Pot Synthesis of a Three-Dimensional Au-Decorated Cellulose Nanocomposite as a Surface-Enhanced Raman Scattering Sensor [128]. (G) AgNFs@MS in SERS detection [129]. (H) Schematic of the working principle of the AEF-SERS platform [124].

3.1.2. Preparation of Nanostructure-Sensitized SERS Substrates

As a mode dependent on the interaction of a rough metal surface with the target molecule for signal output, the sensitivity of SERS often relies on metal-based nanostructures. The designed methods[21,75,135] of nanostructure-sensitized SERS substrates mainly include the following:

1. Sol-Gel Method[102,136]

The sol-gel method can be used to prepare metal nanoparticles or nanocomposites, allowing control over particle size, morphology, and distribution on SERS sensing platform. By adjusting the metal precursors and reductants in the solution, nanoparticles of various shapes (such as spherical, rod-like, etc.) can be synthesized.

2. Chemical Reduction Method[121,137]

The chemical reduction method typically uses the reductant to convert metal salts into metal nanoparticles on SERS platform. For instance, the reductants such as citric acid, sodium borohydride, and hydrogen gas, are used to prepare gold, silver, or other metal nanoparticles. The size and morphology of these nanoparticles can be controlled by adjusting the concentration of reductants, reaction time, temperature, etc.[138]

3. Photolithography and Electron Beam Etching Methods[116,139]

These methods are commonly used to prepare nanostructures with precise morphology and size, such as metal nanorods and nanocolumns. They can precisely control the morphology of the SERS substrate, thereby enhancing the assay performance.

4. Template Method[140,141]

Using polymer templates, silica templates, etc., metal nanoparticles with regular structures can be prepared for SERS design. The template method can prepare the desired metal structures through solvent removal, chemical etching, and is often used to manufacture periodic nanostructures.

5. Thermal Evaporation Method[142,143]

The thermal evaporation method involves heating metal materials to evaporate them and depositing them on a cooled substrate to form metal nanoparticles. This method can be used to prepare gold and silver films, and consequently is commonly used in the preparation of SERS substrates .

6. Solution Chemistry Method[41,137]

The solution chemistry method includes reduction reactions in metal salt solution and SERS surface modification,. By changing the pH value, temperature, and reaction time, metal nanoparticles could be prepared with different shapes and sizes.

7. Electrochemical Deposition Method[102,144]

The electrochemical method reduces metal ions to form nanoparticles on the sensing platform through electrolysis and electrodeposition. This method with good controllability is suitable for the preparation of large-area SERS substrates.

8. Self-Assembly Method[120,145]

The self-assembly method utilizes the self-assembling properties of molecules, nanoparticles, or polymers to generate structures with ordered arrangements on sensing platform. This method is often used to manufacture nanostructures with specific shapes and morphology, suitable for enhancing the Raman effect.

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Generally, the performance of SERS substrates depends on the selection, morphology, and surface structure. Metal nanoparticles, metal nanorods, metal nanoshells, two-dimensional materials, and carbon nanostructures are widely used in the design of SERS substrates. Various synthesis methods, such as chemical reduction, template methods, and photolithography, can control the morphology, shape, and distribution of nanostructures as needed, further enhancing SERS effect.

3.2. Enhancement Behavior of Nanostructure-Sensitized SERS

Benefiting from the merits of nanostructures, Raman signal could be enhanced by the following behavior including electromagnetic enhancement, chemical enhancement, "hot spots" formation; while the nanostructural property and measure model also could affect Raman effect.

3.2.1. Electromagnetic Enhancement Mechanism

The Electromagnetic enhancement (EM) mechanism is an important way to enhance signals. Upon irradiation with light, metal nanostructures induce SPR, resulting in a markedly enhanced electromagnetic field at SERS platform. LSPR (Figure 5A) can significantly amplify the Raman signal of molecules in the vicinity. The enhancement factor ranges from 10^4 to 10^{10} (Figure 5B).

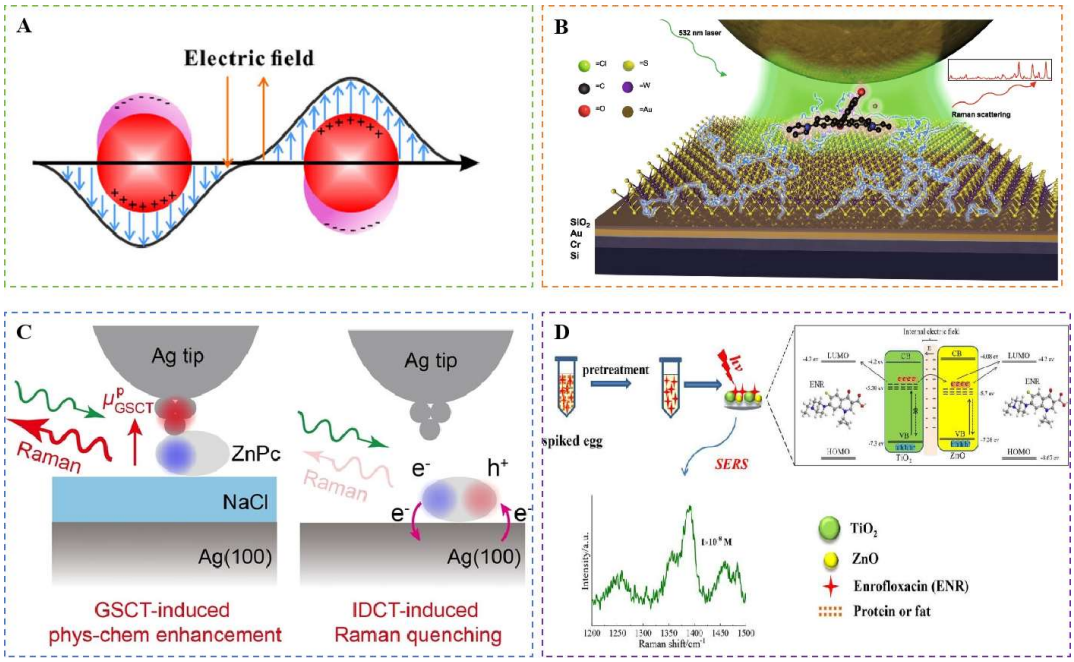

Figure 5. Illustration of (A,B) electromagnetic mechanism (EM)[1,146] and (C,D) chemical mechanism (CM)[147,148] for SERS. HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital; CB, conduction band; VB, valence band.

3.2.2. Chemical Enhancement Mechanism

As one enhancement behavior of nanostructure-sensitized SERS, chemical enhancement (CM) mechanism involves charge transfer (Figure 5C) between the sensing substrate and adsorbed molecules. The enhancement effect typically ranges from 10 to 10^3. This includes non-resonant enhancement, resonant enhancement, and photo-induced charge transfer. As shown in Figure 5D[148], electrons are excited from valence band of TiO_2 and ZnO to their surface state energy levels (Ess), and then transfer to the lowest unoccupied molecular orbital (LUMO) of the ENR molecule for SERS signal enhancement. As depicted in Figure 8D, the Ess of ZnO is lower than that of TiO_2, facilitating the injection of photoexcited electrons from TiO_2 into ZnO and subsequent transfer to ENR's LUMO, forming a "C"-shaped charge transfer pathway. Concurrently, photogenerated holes in ZnO's valence band can migrate to TiO_2. This process effectively inhibits electron-hole

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recombination in TiO_2, providing additional charge transfer to adsorbed molecules and amplifying the SERS signal. Collectively, due to strong interfacial interaction and high carrier concentration, efficient carrier separation from the heterostructure also contribute to the enhanced SERS signal.

3.2.3. "Hot Spots" Formation

In specific regions of metal nanostructures, such as the tips, edges, or gaps, the intensity of the electromagnetic field is particularly high[89,149]. These areas are referred to as "hot spots" （Figure 6A,B）.When molecules are located in these "hot spots", Raman signals are greatly enhanced, which has a significant effect on improving SERS s.

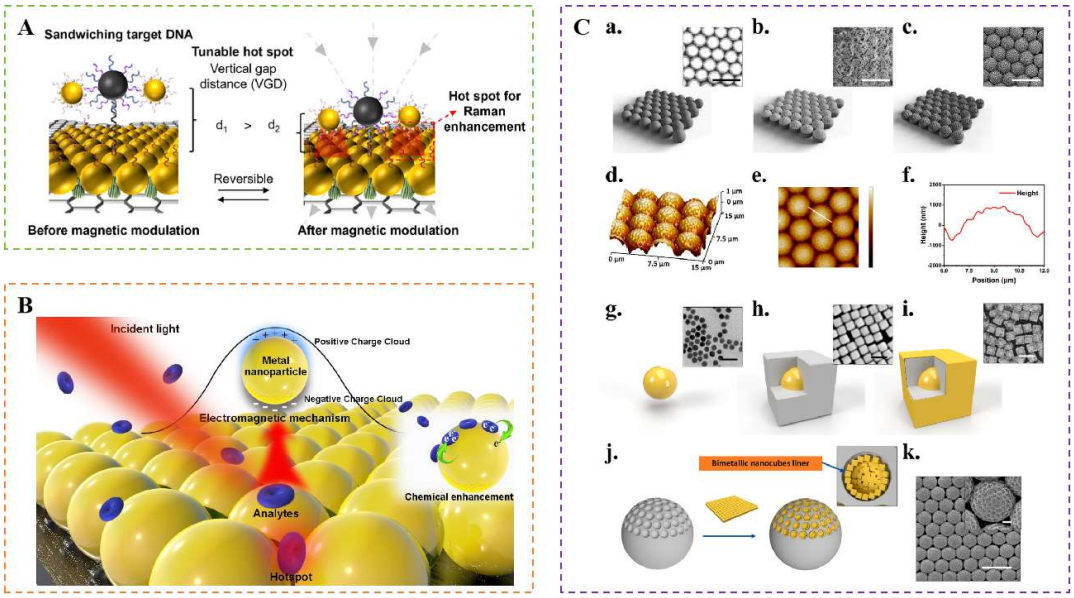

Figure 6. (A,B) Schematic illustration of SERS mechanisms dominated by hotspots, electromagnetic enhancement, chemical enhancement[89,149]. (C) Preparation and characterization of colloidal assembly based 3D SERS substrate[150].

3.2.4. Nanostructural Morphology and Composition on Signal Enhancement

The size and shape of nanostructures have a significant impact on their SERS activity (Figure 6C)[151]. Nanostructures of appropriate size and shape can optimize the enhancement of the electromagnetic field[150], thereby increasing the intensity of Raman signal. The design of nanostructures, such as nanostars, nanorods, and nanoshells, can increase the number and intensity of "hot spots," thereby enhancing the SERS signal. Meanwhile, chemical functionalization of nanostructures (Figure 7) can enhance their interaction with target molecules, improving the sensitivity and selectivity of the Raman signal[152]. By modifying specific functional groups or biomolecules (such as antibodies, aptamers) on nanostructure surface, the recognition toward analytes and signal enhancement can be achieved. Chen et al.[93] constructed a SERS aptamer sensor consisting of signal probe that uses Au@4-MBA@Ag for loading aptamer. In the absence of target analytes, the probes bind to the sensing platform through aptamer duplex formation, creating SERS "hot spots" and strong Raman signal due to surface plasmon resonance.

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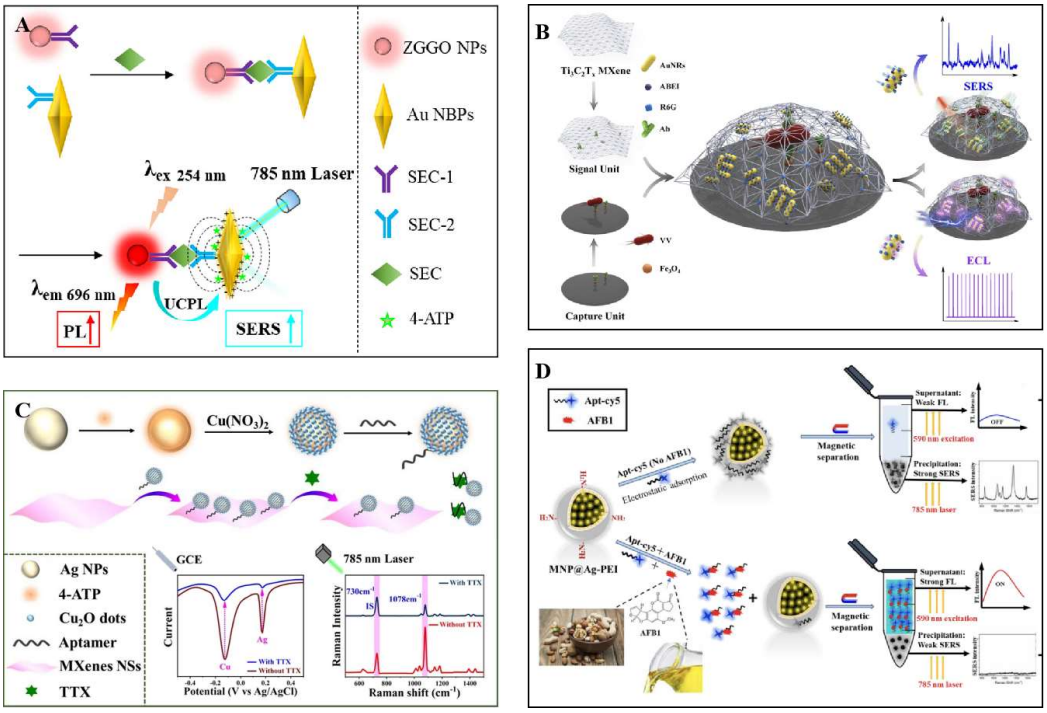

Figure 7. (A) Schematic Illustration of the construction of "Add on" dual-modal optical immunoassay [153]. (B) AuNRs@Ti_3C_2Tx-mediated SERS-electrochemical dual-mode sensor[130]. (C) Schematic illustration of electroactive and SERS-Active Ag@Cu_2O NP-engineered electrochemical/SERS Dual-mode aptasensors[154]. (D) Principle of SERS-fluorescence dual-signal aptasensor for AFB1 determination[155].

In summary, nanostructures could enhance Raman signal through multiple mechanisms including SPR effect, electromagnetic enhancement, chemical enhancement, formation of "hot spots," size and shape effects, surface functionalization, and combination with other detection modes, thereby achieving high-sensitivity and high-selectivity of SERS platform.

3.2.5. Multi-Modal Analysis on Signal Enhancement

With help of nanostructures, SERS can be integrated with other detection modes (such as fluorescence, electrochemistry) to achieve multi-modal analysis, which can enhance Raman signals by leveraging the multiple functionalities of nanostructures (Figure 7). Wei et al.[130] designed a SERS/electrochemiluminescence (ECL) bi-modal sensor for the detection of Vibrio vulnificus（Figure 7B）. The substrate of SERS-ECL dual-mode sensor contains conductive nanostructure with large specific surface area, which can adsorb more AuNPs and in turn improve SERS signal. At the same time, the nanostructure has superior charge transfer capability for SERS signal enhancement . Currently, it has also been found that electrochemical sensing can greatly improve the performance of SERS pattern. To be special, the electrochemical sensing inteface can adsorb or desorb charged substances, allowing for maximum sensing area coverage or desorption of the target. The reproducibility of the SERS substrate is greatly improved.

4. Nanostructure-Sensitized SERS toward Harmful Substances in Food

Food safety incidents not only pose a threat to consumers' health, but also severely hinder the progress of food supply chain. It is widely acknowledged that the development of rapid and reliable technologies ensures the timely identification and control of food hazards. Among the developed patterns, SERS holds potential advantages for non-destructive and rapid detection in food safety evaluation. The physicochemical properties of SERS substrates play important roles in sensing

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performance[89]. However, traditional SERS substrates based on single noble metals suffer from poor sensing stability, limited specificity, and consequently suitable for sensitive detection in complex food scenarios. With the emergence of various functional nanostructures, the development of nanohybrid-sensitized platforms represents a promising frontier for SERS technology in high-sensitivity, interference-free, multiplexing, and reliable food monitoring. The advantages of nanostructure-sensitized SERS for the detection of hazardous substances in food are shown in Table 2.

Table 2. The advantages of nanostructure-sensitized SERS for detection of hazardous substances in food[89,133,134].

Advantage	Description	Advantage	Description
High Sensitivity Detection	SERS technology uses the surface plasmon resonance of metal nanoparticles to significantly enhance the Raman signals of adsorbed molecules, enabling highly sensitive detection of trace hazardous substances in food.	Real-Time Monitoring Capability	Combined with portable devices, SERS technology can achieve real-time monitoring of hazardous substances during food processing and storage.
Rapid Response	SERS technology can provide rapid assay results, which is crucial for immediate response and management of food safety incidents.	Data Traceability	The Raman spectra provided by SERS have unique fingerprint characteristics, aiding in tracing contamination sources and food safety traceability.
No Need for Labeling and Pretreatment	SERS detection does not require complex sample pre-treatment or labeling; it can directly test food samples, simplifying operational process.	Strong Environmental Adaptability	Nanostructures can be used under various environmental conditions, enhancing the application potential of SERS technology in diverse food testing scenarios.
High Selectivity	SERS technology exhibits high selectivity, enabling the rapid quantitative or qualitative detection of hazardous substances in complex food matrices.	Cost-Effectiveness	Although the initial investment may be high, SERS technology reduces the costs associated with repeated testing and erroneous results, making it cost-effective in the long run.
Multiplex Detection Capability	SERS technology is capable of detecting multiple hazardous substances simultaneously, enhancing the efficiency and scope of detection.	Biocompatibility	Selecting appropriate nanostructures ensures that SERS detection is safe for both food and operators, avoiding secondary contamination.

With the merits, nanostructure-sensitized SERS offers a highly potential tool in field of food safety testing.

4.1. Nanostructure-Sensitized SERS Toward Microbial Contamination in Food

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Microbiological contamination remains a urgent issue in the global food safety domain[156,157]. Such contamination encompasses bacteria, viruses, fungi, and parasites, potentially originating from cross-contamination during agricultural production, processing, or transportation[158]. Common foodborne pathogens include *Salmonella*, *Listeria*, *Escherichia coli*(*E. coli*), and *Staphylococcus aureus*(*S. Aureus*)[159,160]. Outbreaks of foodborne diseases not only impact public health but also result in significant economic losses Traditional microbial assay methods, such as culture-based testing and polymerase chain reaction(PCR)[161,162] are highly accurate but often time-consuming, requiring complex preparation. To enhance assay efficiency, researchers have developed rapid methods based on technologies like SERS, ELISA, and electrochemical sensors. In particular, SERS technology has shown immense potential in microbial detection due to its high sensitivity and specificity. Employing metal nanostructures as sensing platform, SERS is capable of detecting microbial markers at single-molecule level. Notably, SERS technology could be applied to perform in non-aqueous environments, which is particularly important for monitoring microbial in low-moisture foods.

4.1.1. Sensing Toward Foodborne Pathogens

Foodborne pathogens are bacteria that can use food as a carrier and produce harmful effects on the body after consumption.[163,164] Foodborne pathogens are considered as the main cause of food poisoning and infectious disease epidemics. Therefore, effective detection of foodborne pathogens is indispensable for safeguarding public health safety. Pan et al.[26] developed a SERS substrate based on gold nanorods for tracing *E. coli* in low-moisture foods (Figure 9A), in which the sensing platform was prepared through physical stamping, magnetron sputtering, and electrochemical deposition for Raman signal enhancement. By conjugating 4-ATP functionalized gold nanorods with antibodies, SERS nano-probes were formed that could specifically recognize antigens on *E. coli* surface. Upon the immunoreaction occurs, they bring enormous nano-probes onto the sensing platform, resulting in the enhancement of Raman spectral signals. The enhancement effect is several orders of magnitude stronger than the unamplified signals (typical SERS enhancement is 10^5–10^6 times).

Zhao et al.[165] fabricated Fe_3O_4@SiO_2-Au nanocomposites with both magnetic and Raman properties, which were used as capture probes to separate bacteria（Figure 8B）. Gold nanostars, due to their multiple sharp branches generating lots of hot spots, exhibit stronger SERS effects compared to gold nanorods or gold nanospheres. By combining graphene oxide (GO) with gold nanostars, the large surface area of GO and the high SERS activity of gold nanostars were leveraged to further improve the sensitivity of bacterial analysis. During the detection process, the construction of a “capture probe/bacteria/SERS label” sandwich structure achieved dual SERS signal enhancement, significantly improving the assay sensitivity toward the target bacteria. Huang et al.[166] proposed a strategy based on polyphenolic chemistry, utilizing metal-phenolic networks (MPNs) to construct SERS nanotags encapsulating silver nanoparticles (AgNPs@4-mercaptobenzonitrile@MPNs)（Figure 8C）. The mentioned MPNs not only serve as a protective layer to improve the stability of SERS tags but also provide non-specific bacterial targeting capabilities due to their interactions with bacterial cell wall components, such as lipopolysaccharides and peptidoglycans. AgNPs with surface plasmon resonance properties, can effectively enhance Raman scattering signals of nearby molecules. Moreover, AgNPs were used as the core of SERS platform, boosting Raman signals through their LSPR characteristics. MPNs, as a protective layer, can reduce the interference of environmental factors on SERS tags, improving the shelf stability of the tags without sacrificing signal intensity. Such protective encapsulation is crucial for the practical application of SERS tags. SERS nanotags combined with MPNs can rapidly and sensitively detect foodborne pathogens, such as *E. coli* O157:H7 and *S. aureus*. These literatures demonstrate the significant role of nanostructures in enhancing Raman signals for bacteria analysis, thereby beneficial for the efficiency of food safety testing.

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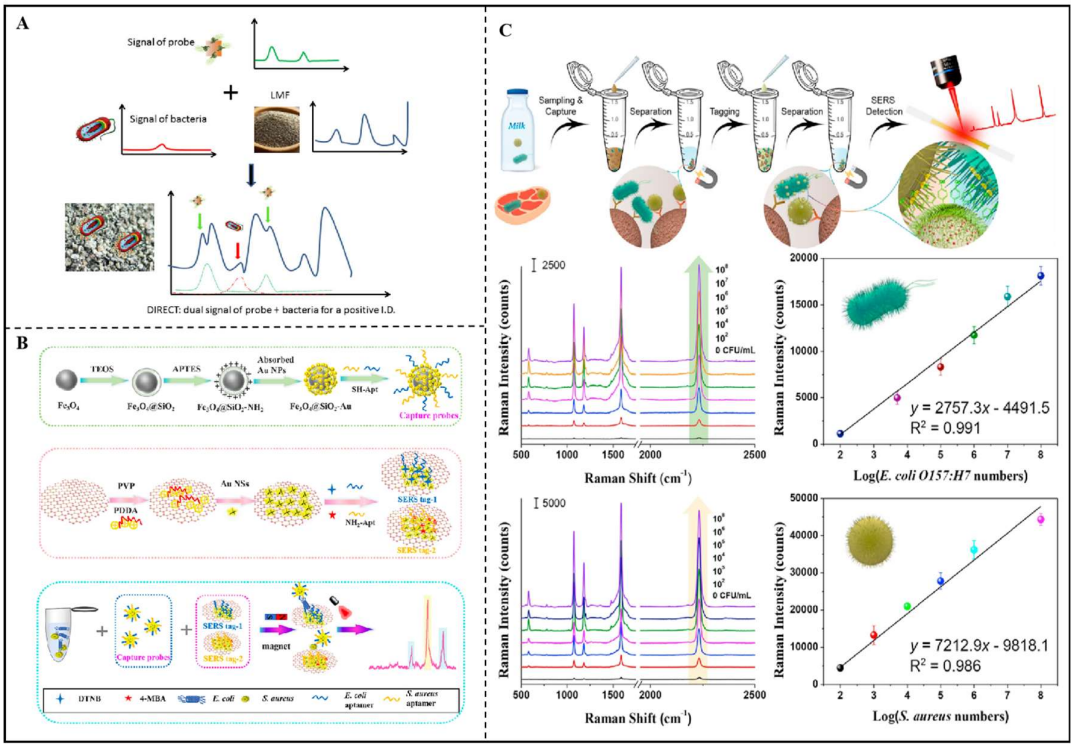

Figure 8. (A) Scheme of the Dual Immunological Raman-Enabled Crosschecking Test assay, identification of peaks attributed to bacteria (red) and probes (green) yields positive detection of food contamination[26]. (B) Schematic diagram of preparation of magnetic capture probes for simultaneously detecting E. coli and S. aureus[165]. (C) Schematic illustration of foodborne bacteria assay with MPN-functionalized SERS tags[166].

4.1.2. Sensing Toward Fungi, Molds, and Their Toxins

SERS is a technique that utilizes metal nanostructures, such as silver and gold, to enhance Raman scattering signal. This technology significantly amplifies the intensity of Raman signal by adsorbing target molecules, such as patulin (PAT), onto the surface of metal nanoparticles. Ma et al.[122] used cysteine (Cys)-mediated nucleophilic addition reaction to detect PAT in apples. The SPR effect of Au@Ag generated a strong electromagnetic field under laser irradiation, which amplified Raman scattering signals of nearby molecules. The formed complex of PAT and Cys anchored to Au@Ag/4-ATP surface, leading to a decrease in Raman signal of 4-ATP (Figure 9A). The variability in signal was inversely correlated with PAT concentration of, allowing for quantitative detection of PAT. The introduction of chemometric algorithms could effectively extract hidden spectral information, improving the predictive performance. Olvera-Aripez et al.[167] used different filamentous fungi (e.g., *Botrytis cinerea*, *Trichoderma atroviride*, *Trichoderma asperellum*, *Alternaria sp.* and Ganoderma sessile) to synthesize AuNPs. In this respect, he SPR absorption of AuNPs is significantly boosted as it was close to the wavelength of the laser, thereby significantly amplifying the Raman scattered light. Using AuNPs synthesized by fungi, the mentioned SERS sensors achieved high-sensitivity assay of specific molecules by enhancing Raman signal. By selecting appropriate fungi and adjusting synthesis conditions, the optimal AuNPs provided a simple, low-cost green alternative pattern for designing SERS platform. In addition, Wei et al.[168] established a sensing platform based on SERS and fluorescence dual-signal for monitoring aflatoxin B1 (AFB1), in which CdTe quantum dots (QDs) were used as fluorescence signal source (Figure 9B). The used AuNPs served not only as sensing substrate for Raman enhancement but also as the acceptor for fluorescence resonance energy transfer (FRET). By combining quantum dot-decorated SiO_2 with AuNPs, satellite nanostructures with high SERS and low fluorescence signals were formed. Furthermore, the surface plasmon resonance effect

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of AuNPs generated a local electromagnetic field enhancement on the of metal nanostructure surface. In the absence of AFB1, the FRET effect between QDs and AuNPs led to the quenching of fluorescence signals. When AFB1 was present, AuNPs could detach from QD-SNPs, resulting in the recovery of fluorescence signals and a decrease in SERS signals. The reported nanostructures improved Raman signal through LSPR and FRET effects, achieving high sensitivity for AFB1 assay. Using Raman signal molecules and fluorescent satellite nanostructures, the technology exhibited excellent sensitivity, accuracy, and stability, and could be applied in actual samples. Xie et al.[169] proposed a tri-mode lateral flow immunoassay based on tailored hollow porous gold nanoflowers (HPGN) for the sensitive detection of AFB1（Figure 9C）. The unique nanostructure of HPGN, possessing hollow and porous nature, provided superior performance compared to traditional AuNPs. As a Raman reporter molecule, 4-MBA was fixed on HPGN surface through Au-S bonding, endowing HPGN with Raman activity. The work constructed an LFIA platform based on HPGN for high sensitivity and selectivity assay of AFB1 through a tri-mode strategy that congregating SERS activity, photothermal effect, and color change.

Yao et al.[154] proposed a dual-mode aptasensor based on electroactive and SERS-active Ag@Cu_2O NPs for tetrodotoxin (TTX) detection (Figure 9D). The Ag@Cu_2O core-shell nanostructures were prepared by depositing a Cu_2O shell on Ag NPs surface. Ag NPs exhibited optimal plasmonic properties in the ultraviolet-visible region, while Cu_2O NPs also showed good Raman properties due to the electron transfer process between Cu_2O NPs and Raman molecules. The Cu_2O shell, with its large dielectric constant, is beneficial for reducing the plasmon attenuation of Ag NPs and improving SERS performance. This dual-mode sensor not only retained the inherent advantages of a single mode but also provided two independent detection signals that, , greatly improving the accuracy of the detection results. The sensor was used for TTX detection in actual samples (fish meat), showing good recovery rates.

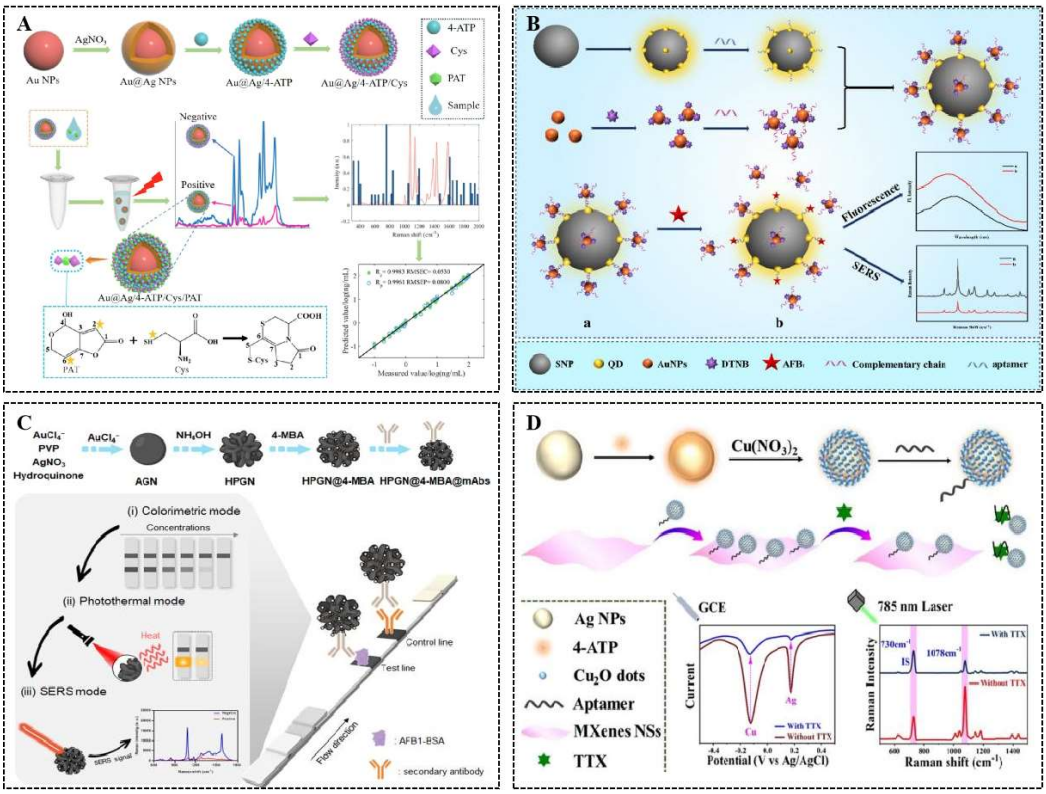

Figure 9. (A) Schematic diagram of SERS toward patulin based on NAR-SERS substrate (Au@Ag/4-ATP/Cys)[122]. (B) Schematic diagram of designing Raman and fluorescence dual-mode aptasensing toward AFB1[168]. (C) Synthesis of HPGN@4-MBA@mAbs and its application in tri-mode LFIA of AFB1[169]. (D)

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Schematic Illustration of electroactive and SERS-Active Ag@Cu_2O -engineered electrochemical/SERS dual-mode aptasensing toward tetrodotoxin[154].

4.1.3. Sensing Toward Viruses

Peng et al.[170] combined Ag@Au core-shell nanoparticles and hybridization chain reaction (HCR) to achieve highly sensitive detection of hepatitis C virus (HCV) nucleic acids (Figure 10A). Using strong SERS activity of AgNPs with chemical stability of AuNPs, a strong electromagnetic field was generated through surface plasmon resonance effects for Raman scattering signal enhancement. Upon binding of the target HCV nucleic acids to Ag@AuNPs, the HCR reaction was triggered, further enhancing SERS signal. By recording the signals with Raman spectrometer, high-sensitivity and selective detection of HCV nucleic acids was achieved. Y Park et al.[34] constructed a signal amplification system based on SERS for the detection of norovirus (NoV) (Figure 10B).The system employed Au/Ag core/shell satellite nanostructures, in which this structural design improved electromagnetic field intensity 4-MBA served as a Raman tag for signal output. By integrating magnetic nanoparticles (MNPs) with anti-NoV antibodies, a sandwich structure was formed to capture NoV, enabling concentration-dependent SERS signal detection. The system exhibited a detection limit of 0.76 fg/mL for NoV-like particles (NoV-LP), which was approximately 10^7 times more sensitive than commercial ELISA kits. This SERS-based system demonstrated the potential for highly sensitive detection of Norovirus. Wu et al.[171] synthesized silver nanoparticles with specific SPR properties by chemical reduction. These particles could generate a strong electromagnetic field under laser irradiation, enhancing Raman scattering signal of nearby molecules. By covering silver surface with gold shell to form core-shell structure (Ag@AuNPs), SERS signal was improved. Notably, methanol solvent was introduced into an aqueous system of silver nanoparticles containing iodide ions. Methanol acted as an anticoagulant to maintain the system stable at low temperatures and improved the nanoparticles' ability to form "hotspots," which was suitable for virus detection. By introducing the virus sample to SERS substrate, the interaction between virus molecules and nanoparticles could form "hotspots," enhancing Raman signal of virus molecules. The study successfully obtained stable SERS signals of biomolecules at -20°C low-temperature conditions, which was particularly important for virus assay on cold chain food packaging (Figure 10C).

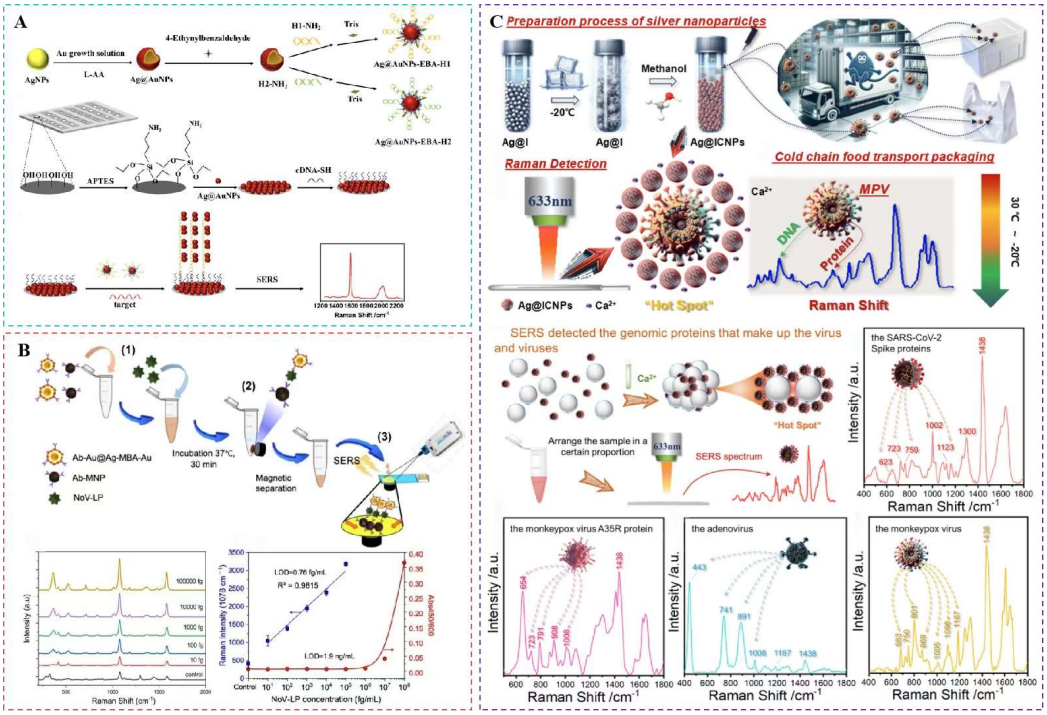

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Figure 10. (A) Schematic illustration of (a) construction of SERS probes, (b) preparation of the assay plate, and (c) SERS-sensing principle[170]. (B)Detection of NoV-LP in PBS using Palmtop Raman spectrometer[34]. (C) Schematic Diagram of designng silver-enhanced substrate, outer packaging of cold chain transportation, and conceptual schematic diagram of relationship between virus sample and "hot spots"generated by silver-enhanced substrate, SERS toward genomic proteins[171].

4.2. Nanostructure-Sensitized SERS toward Chemical Contamination in Food

The effective analysis of chemical contamination is an essential component of food safety, involving the assay of pesticides, veterinary drugs, and their metabolites in agricultural and livestock products[15]. Technologies[172–174]such as high-performance liquid chromatography (HPLC), gas chromatography (GC), liquid chromatography-mass spectrometry (LC-MS), and gas chromatography-mass spectrometry (GC-MS) have been widely applied in monitoring chemical contamination. Emerging detection technologies like SERS have garnered attention for their high sensitivity and rapid response capabilities. However, enhancing the sensitivity and selectivity of Raman pattern for certain low-concentration or structurally similar compounds remains a challenge. With the advancement of chemometrics and machine learning technologies, the data analysis capabilities of Raman spectroscopy have been strengthened, improving the assay accuracy[175,176]. More comprehensive Raman spectroscopy databases and standard libraries could support the identification and quantification of more compounds. The efficient sample pretreatment and analysis methods offered useful tools for simultaneous detection of multiple agrochemical and veterinary drug residues at ppt (part-per-trillion) level[89,177].

4.2.1. Sensing Toward Pesticide Residues

He et al.[178] proposed a droplet trapping band-based SERS pattern for r monitoring contaminants in food. Gold nanostructures (Au nanodendrites) with sharp edges and tips was exploited as sensing substrate by electrochemical deposition (Figure 11A), providing abundant SERS hotspot regions. A strip with specific micropores was designed to capture and enrich the target substances in microdroplets via capillary action, thereby amplifying Raman signal. The wettability difference between micropores and gold nanostructures allowed for rapid capture and fixation of microdroplets, facilitating direct sample collection from food surfaces. The large surface area and three-dimensional structure of gold nanostructures further amplified Raman signals, enabling high sensitivity and convenient assay of pesticide residues. Hu et al.[120] detailed SERS pattern for pesticide residue detection based on self-modeled mixed analysis (SMA). The high-density array of gold nanorods was used as SERS substrate via organic-water interfacial self-assembly method (Figure 11B). The SMA mode processed the spectral data of mixed pesticides to extract pure component spectra. By contacting pesticide residues on fruits' surface with SERS substrate, the useful strategy exhibited good performance for rapid and non-destructive assay of mixed pesticide residues on fruit surfaces through the formation of hotspot regions. Wang et al.[84] described a assay pattern that used metal nanostructures to enhance Raman signals. The SERS substrate was designed by assembling gold cores on polystyrene microspheres, modifying the surface with a Raman internal standard (1,4-benzenedithiol), and subsequently growing a gold shell on this internal standard (Figure 11C). Three-dimensional hotspot regions were constructed, primarily located between the hydrophobic gold film and the composite particles, as well as between the particles and within the core-shell structure. The enhancement of SERS signal primarily arose from electromagnetic effect, where localized surface plasmon resonance occured when light frequency matched the oscillation frequency of electrons,. The hydrophobic interface facilitated the enrichment and capture of analytes. This mode demonstrated high sensitivity and stability in tracing pesticide residues on the surfaces of cucumbers, apples, and fish, s beneficial for low-cost and effective SERS platform toward various pesticide residues. Chen et al.[83] used golden decahedral nanoparticles (Au DNs) with special geometries as SERS active substratesby seed growth method, which made them produce multiple "hot spot" regions(Figure 11D). In the experiments, Au DNs were employed to detect six types of triazole

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pesticide residues on the surfaces of beans, apples, and vegetables, verifying significant potential for real sample assay with in-situ and multiplex pattern.

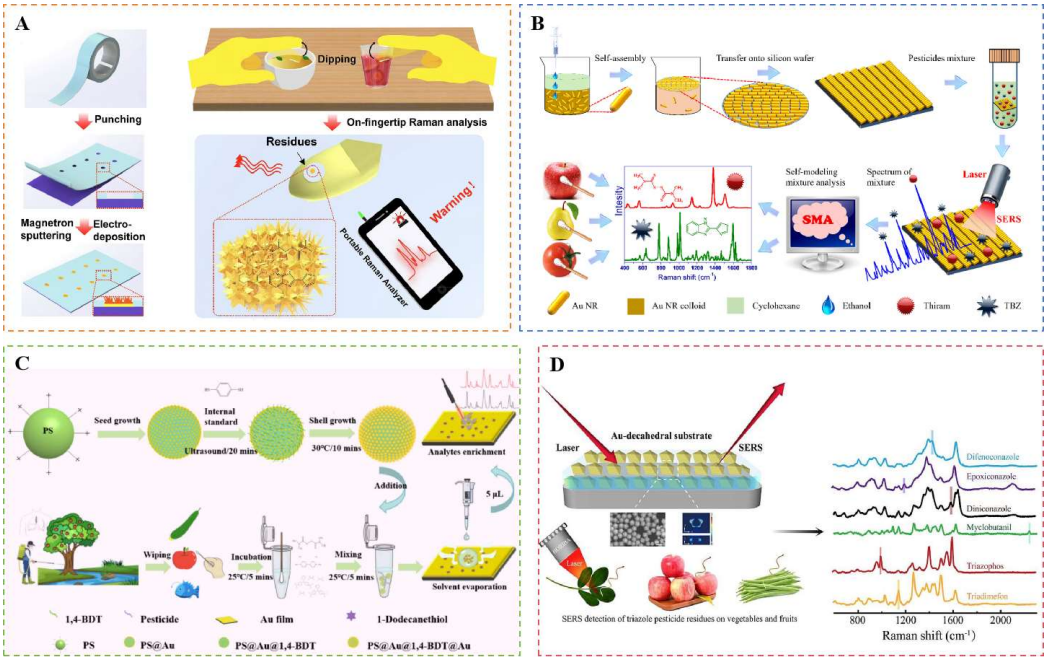

Figure 11. (A) Tape-based SERS sensors toward on-hand detection of food contaminants[178]. (B) Schematic of interfacial self-assembly of Au NRs array toward multiple pesticides on fruit surface based on SERS and self-modelling mixture analysis [120]. (C) The schematic of PS@Au@1,4-BDT@Au synthesis and pesticide detection[84]. (D) Illustration of Au decahedral nanoparticles for SERS assay of triazole pesticide residues in vegetables and fruits[83].

4.2.2. Sensing Toward Veterinary Drug Residues

Liang et al.[42] introduced spiky gold-silver nanoparticles (spiky Au@Ag NPs) and bismuth ditungstate (Bi_2WO_6) composite membranes as SERS platform, which were used for detecting a variety of pesticide and veterinary drug residues with high sensitivity (Figure 12A). Gold nanoparticles were synthesized through a chemical reduction method, and a silver shell was grown on Au surface, forming a spiky structure rich in "hotspot" regions for electromagnetic field enhancement. The incorporation of Bi_2WO_6 further improved SERS signal and promoted charge transfer from spiky Au@Ag NPs to target molecules through forming "donor-bridge-acceptor" system, thereby amplifying SERS signal. The composite film was validated for its high sensitivity in detecting pesticide and veterinary drug residues in real samples. Wang et al.[177] introduced a Janus-labeled AuNPs-based SERS technique combined with immunochromatographic assay (ICA) for monitoring veterinary drug residues (Figure 12B). The Janus-labeled Au nanoparticles had two functional regions: a monoclonal antibody for the specific recognition of target molecules and a DTNB molecule for SERS signal output. This design allowed the nanoparticles to produce a strong SERS signal when recognizing target molecules such as sulfamethazine (SM2). The precise fabrication of nanogaps created hotspot regions that enhanced SERS signal. By integrating ICA technology, this method achieved rapid, quantitative, and ultrasensitive detection of SM2 residues in milk. Experimental validation demonstrated that this method exhibited high sensitivity, easy to operate, and rapid results, indicating its good application prospects.

Hu et al.[179] described a magnetic Fe_3O_4-WO_3-X@AuNPs sensing toward albendazole (ABZ) and streptomycin (SPT) in meat samples（Figure 12C）. The prepared Fe_3O_4-WO_3-X@AuNPs enhanced SERS signal through EM and CM, in which AuNPs provided EM enhancement and WO_3-X contributed to CT enhancement. The recognition mechanism between the sensor and target

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molecules was investigated through charge transfer model. The magnetic properties of Fe_3O_4-WO_3-X@AuNPs allowed for rapid separation and enrichment of target molecules, reducing interference from the sample matrix and improving the accuracy of SERS analysis. The experimental results indicated that this method held promising applications for the rapid, sensitive, and selective assay of veterinary drug residues in meat, well qualified for monitoring food safety. Li et al.[41] introduced a dual-mode pattern to construct AuNPs/Cu-TCPP(Fe) nanosheets with peroxidase activity and SERS effect, which combined with colorimetric and SERS sensing toward veterinary drug residues. The strategy was applied to detect LEV in actual milk sampleswith good recovery rates and stability. Tu et al.[180] introduced a SERS label (MDAu@Ag) to enable the simultaneous detection of multiple veterinary drug residues in complex samples (Figure 12D). The nanostructure tag consisted of three components: a 200 nm Fe_3O_4 magnetic core with strong magnetic responsiveness; a 1 nm PEI interlayer for built-in nanogaps and multiple efficient hotspots; and two layers of Raman reporter molecules (DTNB and MBA) for SERS signal amplification. The application of MDAu@Ag in LFA system allowed for the direct capture of target drug residues from real food samples, thus eliminating cumbersome pretreatment process and improving assay sensitivity. Additionally, spiking recovery experiment was conducted to validate the reliability of SERS pattern, showcasing strong potential for practical applications.

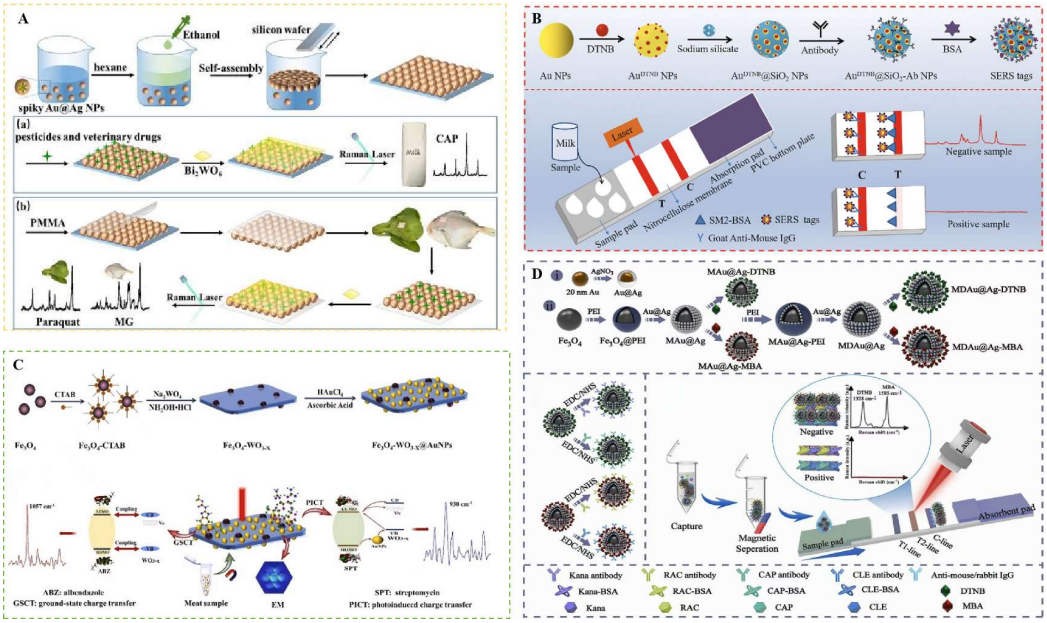

Figure 12. (A) Schematic illustration of spiky Au@Ag NPs-Bi_2WO_6 film for SERS sensing toward pesticides and veterinary drugs[42]. (B) Schematic diagram of SERS-ICA based on mAbAuNpDTNB nanostructures. (a) The preparation process of mAbAuNpDTNB SERS tags. (b) Schematic testing process of the SERS-ICA strip for SM2[177].(C) Fe_3O_4-WO_3-X @AuNPs for SERS sensing toward albendazole and streptomycin in meat samples via magnetic separation-enrichment-detection all-in-one[179]. (D) Schematic representation of (a) synthesis of (i) 24 nm Au@Ag NPs and (ii) multilayered MDAu@Ag tags with dual layers of Au@Ag and Raman dyes, (b) preparation of immuno-MDAu@Ag SERS tags, and (c) design of MDAu@Ag-based SERS-LFA for simultaneous detection of four veterinary drugs[180].

4.2.3. Sensing Toward Heavy Metals

Heavy metal ions are easy to enter food and drinking water through natural environmental pollution, industrial emission, and chemical fertilizer[181,182]. Owing to the high toxicity, easy enrichment, difficult degradation of heavy metals, it is necessary to develop effective strategy toward heavy metal monitoring[183,184]. Li et al.[123] used Au@Ag NPs and covalent organic frameworks

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(COFs) complexes as SERS substrates (Figure 13A). Au@Ag NPs generated strong electromagnetic fields (E-fields) on COFs surface, in which the large specific surface area and high adsorption capacity of COFs contributed to E-fields enhancement for SERS signal amplification. Y-shaped DNA (containing two embedded probes, Y1 and Y2) was used to shorten the distance between Raman tag and SERS substrate, thereby enhancing the coupling effect of E-fields and improving assay sensitivity. The sensor exhibited good recovery for monitoring Hg^{2+} in real samples. Chen et al.[185] used the functional AgNPs to trace Mn^{2+} (Figure 13B). In the presence of Mn^{2+}, MNA-MA-AgNPs aggregated and then reduced the distance between noble metal particles, thereby enhancing the SERS signal. This enhancement behavior was due to the so-called "gap hotspots effect", in which the intensity of the electromagnetic field increased obviously.[186]

Mohamed[187] applied the special structure and SERS activity of helical CNTs to achieve high sensitivity and selectivity for detecting heavy metal ions (Hg^{2+}/Cd^{2+}) in water. The formed structure of spiral CNTs on the screw nail surface increased the number of SERS-active hot spots,. The chemical modification of CNTs could improve their adsorption capacity for metal ions through chemical bonding. Dong et al.[137] proposed a novel magnetic SERS tag (Fe@RAu) for ultrasensitive immunochromatographic detection (ICA) to monitor cadmium ions (Cd^{2+}) in complex samples. The combination of a large Fe_3O_4 core and a coarse gold shell provided a robust magnetic response and high SERS activity (Figure 13C), enabling a fast, low-cost sensing toward heavy metal contamination in aqueous environment.

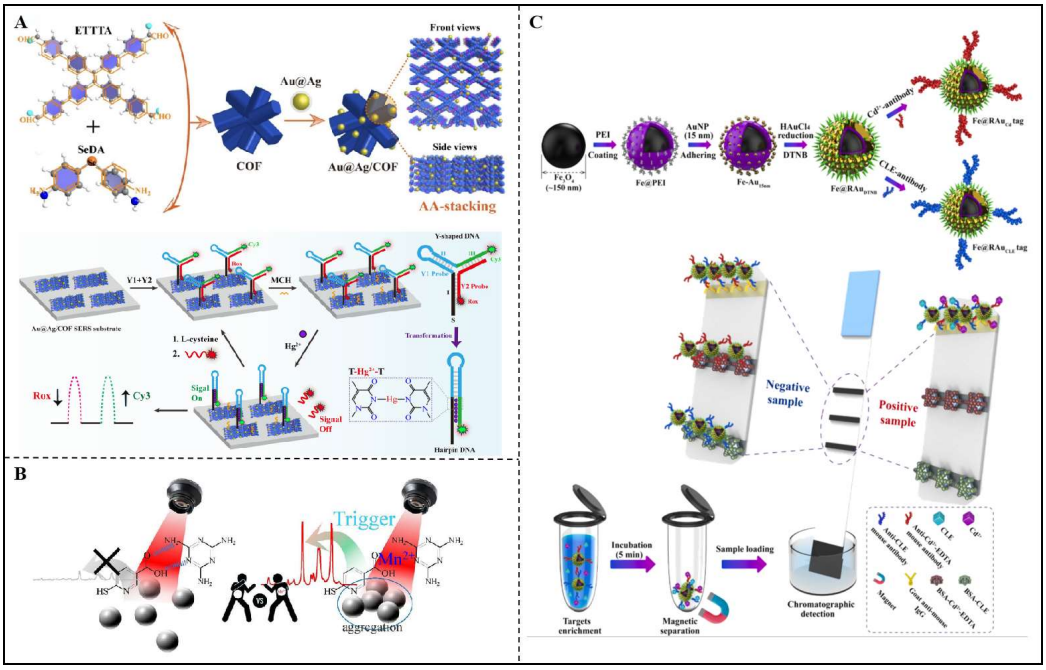

Figure 13. (A) Schematic illustration of dual-signaling SERS ratiometric platform for Hg^{2+} detection[123].(B) Schematic diagram of Mn^{2+}-induced aggregation of MNA-MA-AgNPson SERS sensing toward Mn^{2+}[185]. (C) Schematic of DTNB-embedded Fe@RAu on MagSERS-ICA toward simultaneous monitoring of CLE and Cd^{2+} in complex samples[137].

4.2.4. Sensing Toward Food Additives and Illicit Adulterants

Food additives are a type of natural or chemical synthetic substances to improve the food flavor, texture, and storability. The normal use within the permitted range does not cause harm to humans; but exceeding usage limit, it can be toxic and carcinogenic effects on humans[188]. Hence, it is important to develop rapid screening technology for food additives. Ramachandran et al.[189] exploited the special structure of ZnO nanorods and Ag nanotriangles to achieve high sensitivity and

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selectivity for detecting food additive 2,6-di-tert-butyl-p-hydroxytoluene (BHT) through synergistic effect of CT and EM effects. ZnO nanorods, grown on stainless steel substrate via hydrothermal synthesis, possessed high surface-to-volume ratio, chemical activity, and the ability to directly transfer charge carriers. Ag nanotriangles were sensitized on the surface of ZnO nanorods to boost electromagnetic field coupling and amplification of local fields, thereby achieving a multi-fold sensitivity increase in sensitivity. The junctions between ZnO nanorods and Ag nanotriangles promoted charge transfer and the enhancement of electromagnetic fields, holding significant importance for ensuring food safety.

Li et al.[107] applied precious metal nanostructures such as gold and silver as SERS substrates for the detection of trace additives and contaminants in food. By controlling the shape, size, and arrangement of metal nanostructures, the effect of local electromagnetic fields could be enhanced. Modification of specific molecules or ligands onto metal nanostructures could improve selectivity and sensitivity for the analytes, in which surface plasmon resonance occurred when irradiated with specific light wavelengths for Raman signal output. Lu et al.[190] designed the heterostructure (AgNTs/TNA) composed of silver triangle nanoparticles (AgNTs) and TiO_2 nanorod arrays (TNA) as the active SERS substrate toward sensing food additives.. AgNTs, with their sharp edges, strongly improved the local electromagnetic field for creating effective hotspots. TNA contributed to forming strong electromagnetic enhancement areas. The combination of AgNTs and TNA provided both electromagnetic and chemical mechanism effects. Additionally, AgNTs/TNA heterostructure could generate electrons and holes that reacted with oxygen to produce superoxide radicals, oxidizing and breaking down probe molecules, allowing for substrate regeneration and reusability.

Hu et al.[87] utilized a pNIPAM@Au NRs (poly(N-isopropylacrylamide)@Au NRs) nanocomposite with temperature-controlled, tunable plasma behavior and long-term stability as SERS substrate (Figure 14A). Under laser irradiation of a specific wavelength, gold nanorods could act as photothermal converters to quickly generate local heating, triggering the phase transition of pNIPAM. By controlling the loading of Au NRs on pNIPAM template, the optical properties and SERS performance were improved to detect the illicit additive Malachite Green (MG) in aquatic products (Figure 14B). Under the optimal the temperature and laser wavelength, the sensitive detection of MG was achieved with detection limit of 0.73 ng g^{-1} (Figure 14C), which met the minimum required performance limit (MRPL) set by the European Commission. Xu et al.[191] exploited femtosecond laser-induced plasma-assisted ablation (fs LIPAA) to prepare SERS substrate for monitoring contaminants such as melamine in food. Silicon nanoparticles were generated on glass substrates by fs LIPAA technology, and then silver thin films (Ag NPs/glass) were deposited on them by electron beam evaporator to form hot spots with high uniformity. Wang et al.[192] achieved a highly sensitive detection of PAE plasticizers in food additives by designing a specific combination of two-dimensional silver plates and nano-silver sols(Figure 14D). This silver plate provided a homogeneous metal surface that amplified Raman signal of sample molecules. The sol of silver nanoparticles was used as synergistic agent with 2D silver plates to further enhance Raman scattering. The addition of silver nanoparticles increases the number of hot spots in the system, thereby increasing the intensity of the Raman signal. Li et al.[107] utilized a portable Raman spectrometer (Figure 14E) to compare the changes in Raman spectral characteristic peaks of pure persimmon cakes and adulterated persimmon cakes; machine learning was employed for rapid qualitative assay of titanium dioxide adulteration on the surface of persimmon cakes. This method was not only non-destructive but also highly accurate, making it suitable for on-site analysis.

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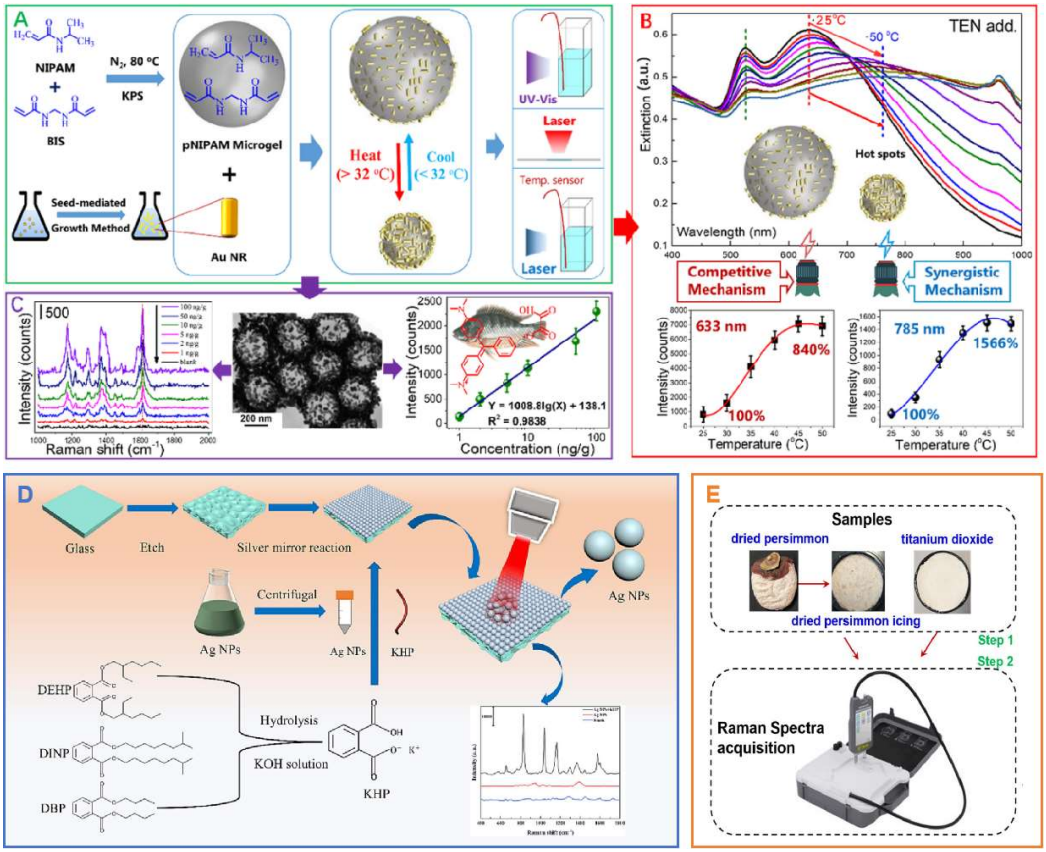

Figure 14. Preparation of pNIPAM@Au for optical and SERS analysis. (A) Fabrication and characteristic procedures of pNIPAM, Au NRs, and pNIPAM@Au NRs[87]. (B) Synergistic versus competitive mechanism of SERS (hot-spots) and SERRS (LSPR bands matching) effect when using 785 nm (NIR range) and 633 nm (Vis range) laser excitations at swollen (25℃) or collapsed (50 ℃) states[87]. (C) Detection of MG in fish tissues using pNIPAM@Au as SERS substrates[87]. (D) Schematic diagram of SERS sensing toward plasticizer in oil[192]. (E) Schematic diagram of detection of titanium dioxide adulteration in persimmon frosting [107].

4.3. Nanostructure-Sensitized SERS Toward Physical Contamination in Food

Physical contamination in food refers to the pollution of food by non-biological and non-chemical substances, which may affect the safety and quality of food and even pose a threat to human health. Table 3 lists some of the common types of physical contamination found in food.

Table 3. Common types and sources of physical contamination in food[193–195].

Classification		Sources
Foreign matter contamination		Metal fragments, glass fragments, plastic fragments, stones, sand particles, and more. May originate from wear of processing equipment or packaging materials, environmental pollution during raw material collection or processing.
Radioactive contamination		Contamination caused by radioactive substances, which may enter the food chain through soil and water sources.

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Noise pollution		Long-term exposure to noise may impact the work efficiency and psychological health of food processing personnel, indirectly affecting food quality.
Light pollution		Excessive lighting may affect food storage conditions, leading to spoilage or a decrease in nutritional value.
Thermal pollution		Inappropriate temperatures may cause food spoilage during storage and transportation.
Mechanical impurities		Lubricating oils, metal shavings, and other substances from mechanical equipment may be mixed into food.
Packaging material contamination		Certain chemicals from packaging materials may migrate into food, causing physical contamination.
Natural impurities		Naturally occurring impurities in food raw materials, such as small stones in grains, small insects in fruits and vegetables, etc.
Human negligence		During food processing, tools, equipment parts, and other foreign objects may be inadvertently mixed into food due to human error.

Microplastic, as a kind of plastic particles smaller than 5 mm but larger than 0.1 μm, is considered as a threat to foods and beverages. Identification of microplastic particles from complex matrices can be challenging due to their various sizes, shapes, and polymer types. Yu et al.[17] exploited a liquid-liquid interface strategy to assemble micro-/nanoplastics and gold nanoparticles (GNPs) into dense and uniform plasma arrays (Figure 15A), thereby enabling rapid and sensitive detection of trace nanoplastics . To be special, Ethyl acetate was selected as the organic phase to participate in self-assembly process due to its polarity being close to that of water, which helpd to accelerate the self-assembly process and produce the strongest SERS signals. The presence of micro-/nanoplastics effectively promoted the self-assembly process of GNPs at oil-water interface, increasing the number of molecules in hot spots for SERS signal amplification. The aromatic rings in micro-/nanoplastics interacted strongly with the gold nano-surface through π-metal interactions,

 doi:10.20944/preprints202501.1938.v1

promoting the adsorption of more micro-/nanoplastics at liquid-liquid interface. The PCA algorithm was utilized to process SERS data to distinguish and identify various micro-/nanoplastics components in aquatic environments as well as in edible oils (Figure 15B).

Song et al.[62] took advantage of the difference between fish bones and fish meat on Raman spectra, and achieved high sensitivity and high accuracy for discerning fish bones in fish meat (Figure 15C). The Fuzzy Rough Set Model (FRSTCA) based on Thermoelectric Charge Algorithm was used to select the optimal wavelength, and the Support Vector Data Description (SVDD) model was established for the detection of fishbones. Spectral Angle Mapping (SAM) images were converted to binary images for distinguishing fishbone pixels and backgrounds. By calculating the number of pixels of each component in the binary image and correlating it with the actual component concentration, the quantitative detection of fish bones was realized. This technology could effectively detect fish bones with a depth of less than 2.5 mm, and the assay accuracy reached 90.5%, provided a useful technical means for food safety testing.

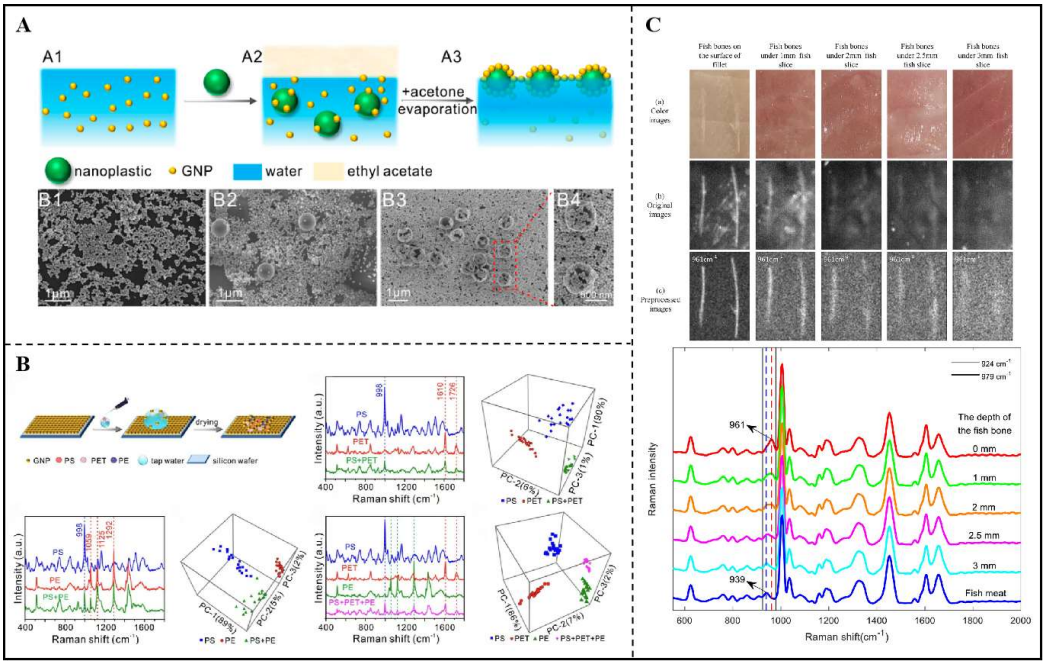

Figure 15. (A) Illustration of LICA of Plasmonic GNPs and Nanoplastics. (A1) Before Coassembly, GNPs Were Distributed in the Bulk Aqueous Solution. (A2) Adsorption Behavior Occurred between GNPs and Nanoplastics. (A3) Coassembly of GNPs and Nanoplastics at the Ethyl Acetate−Water Interface Induced by Acetone. (B1−B3) SEM Image Corresponding to A1−A3. (B4) Enlarged SEM Image of B3[17]. (B) Schematic diagram of simultaneous detection of multi-component nanoplastics in tap water using liquid interfacial array transferred to a silicon wafer[17]. (C) (a) color image, (b) original, and (c) preprocessed Raman images at 961 cm^{-1},Preprocessed Raman spectra of fish meat and fish bones (at different depths)[62].

5. Conclusions

In this review, we discuss the important role of nanostructures in enhancing Raman signals, in particular the application of nanostructure-sensitized SERS in food safety evaluation. By analyzing the latest research findings, this review summarizes the critical role of nanostructures in SERS technology and how they can help improve the efficiency and accuracy. In addition, nanostructures has also promoted the application of SERS technology in conjunction with other assay technologies, providing an efficient and low-cost solution for food safety testing. The application of nanostructures in SERS technology not only improves the efficiency and accuracy of food safety assay, but also provides new ideas and directions for the development of food safety evaluation technology in the

 doi:10.20944/preprints202501.1938.v1

future. With the continuous progress of nanostructure technology and the continuous improvement of SERS technology, its application prospect in food safety testing will be broader.

Author Contributions: Z.L. is the leading author and prepared this review paper. R.Y. and H.C. provided critical feedback. X.Z. provided critical feedback and revised this review. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: Thank you to my mentors and fellow students for their support.

Conflicts of Interest: The authors declare no conflict of interest.

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