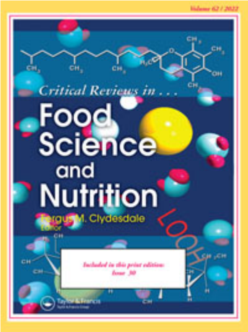

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REVIEW

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Flexible surface-enhanced Raman scatting substrates: recent advances in their principles, design strategies, diversified material selections and applications

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ABSTRACT
Surface-enhanced Raman scattering (SERS) is widely used as a powerful analytical technology in cutting-edge areas such as food safety, biology, chemistry, and medical diagnosis, providing ultra-fast, ultra-sensitive, nondestructive characterization and achieving ultra-high detection sensitivity even down to the single-molecule level. Development of Raman spectroscopy is strongly dependent on high-performance SERS substrates, which have long evolved from the early days of rough metal electrodes to periodic nanopatterned arrays building on solid supporting substrates. For rigid SERS substrates, however, their applications are restricted by sophisticated pretreatments for detecting solid samples with non-planar surfaces. It is therefore essential to reassert the principles in constructing flexible SERS substrates. Herein, we comprehensively review the state-of-the-art in understanding, preparing and using flexible SERS. The basic mechanisms behind the flexible SERS are briefly outlined, typical design strategies are highlighted and diversified selection of materials in preparing flexible SERS substrates are reviewed. Then the recent achievements of various interdisciplinary applications based on flexible SERS substrates are summarized. Finally, the challenges and perspectives for future evolution of flexible SERS and their applications are demonstrated. We propose new research directions focused on stimulating the real potential of SERS as an advanced analytical technique for commercialization.

KEYWORDS
Biosensor; cell culture; design approaches; environmental pollutant detection; flexible SERS; food safety; medical diagnostics

Introduction

Surface-enhanced Raman spectroscopy (SERS) as an ultra-sensitive vibrational spectroscopy technology has attracted considerable attention because of its outstanding characteristics in fingerprint identification, ultra-high resolution, ultra-strong anti-interference ability, ultra-fast response speed, nondestructive feature to samples. For this reason, SERS technology has been extensive demonstrated and utilized in a wide variety of fields, especially the newly emerging interdisciplinary and cross cutting-edge fields (Liebel et al. 2020; Plou et al. 2020; Zong et al. 2018). Although SERS technology and its related applications have made amazing achievements, there is still no unified consensus on the physical mechanism behind it (Ding et al. 2017). Electromagnetic enhancement and chemical enhancement are the two main enhancement mechanisms accepted by the academic community, among which the explanation of electromagnetic enhancement mechanism accounts for the majority (Tong, Zhu, and Liu 2011; Gu et al. 2013; Ding et al. 2016). During the development and application of Raman technology, excellent SERS substrates are important driving force in extending their application scopes and potentials, thus there has been much emphasis on how to prepare SERS substrates with high Raman-enhanced activity. To this end, the SERS activity and SERS enhancement performance can be significantly improved by selecting appropriate materials, orderly and controllable surface roughness, increasing particle uniformity and accurately controlling particle gap (He, Wu, et al. 2021; Xu, Ding, et al. 2021).

The target (or molecule of interest) to be detected generally needed to be attached to surface of plasmonic nanopatterned arrays via physical and chemical adsorption to achieve effective recognition (Guo et al. 2020; Kou et al. 2020). The enhancement of the electromagnetic field in SERS is a two-step process. In addition to the local enhancement of the plasmonic nanoparticles at the incident frequency, the Raman polarizability derivative of the target molecule-plasmonic nanoparticles system also has an enhancing effect. More importantly, the electromagnetic field around the plasmonic material is not uniformly distributed, but highly localized in narrowly spatial regions (SERS hot spots) (Ding et al. 2016). Therefore, to maximize the detection sensitivity, it is urgent for the target molecules to be tightly attached (or adsorbed) to the precious metals, especially at the interface of its hot spot areas. It is conceivable,

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however, that this is quite difficult for rigid SERS substrates because they lack sufficient flexibility and bending properties to adhere closely, which greatly reduces their ability to detect directly in situ on non-planar surfaces of fruits, vegetables, animal skins, processed foods. Besides, for some pigments that cannot dissolve works of art or precious items (such as national treasures), irreparable damage will be caused to them when analyzing and excavating their hidden secrets through rigid SERS substrates. Although the detection methods based on rigid SERS substrates have been widely used in laboratory analysis, their applications are limited by tedious operational steps and the requirements of skilled technicians (Roh et al. 2016). Therefore, it is of great significance to deeply study the construction of SERS substrates based on inexpensive and tunable flexible materials. In contrast, flexible SERS substrates should have the advantages of stretch-ability, fast response, adjustable shape, wear resistance, convenience (Huang, Li, et al. 2020). More importantly, the detection sensitivity could be significantly enhanced by utilizing flexible SERS substrates because of their close adsorption with the targets to be detected.

A large number of materials (or matrixes) have been used to construct flexible SERS substrates, including but not limited to fibrous paper (Wang, Liu, and Dou 2016), cellulose (Song, Zhang, et al. 2021), graphene/graphene oxide (Pérez et al. 2016; Sun, Liu, et al. 2017; Zhao, Xiao, et al. 2018), carbon nanotubes (Tian, Zhang, et al. 2019), and polymers (Ding et al. 2020; Nowicka et al. 2019; Hao et al. 2020; Kim et al. 2017). These prepared flexible SERS substrates can encapsulate complex surfaces for fast response detection, and can also be arbitrarily tailored to arbitrary shapes and sizes, which greatly promote its applications for in situ detection, real-time on-site analysis and monitoring, nondestructive testing, and preparing wearable devices. Some review papers based on flexible SERS substrates have been reported (Zhang, Chen, et al. 2021; Xie, Pu, and Sun 2018; Xu et al. 2019; Restaino and White 2019). For instance, recent advances in flexible SERS substrates for nondestructive food detection were summarized (Zhang, Chen, et al. 2021). Nanofabrication techniques for SERS substrates and their applications in food safety analysis were overviewed (Xie, Pu, and Sun 2018). Flexible SERS sensors in applications of point-of-care diagnostics were reviewed in Xu et al. (2019). A critical review of flexible and porous SERS sensors for analytical chemistry at the point-of-sample was demonstrated by Restaino and White (2019). However, there is still a lack of comprehensive overview of the flexible SERS substrates in this field for further development.

In this review, we provide an in-depth summary of flexible SERS substrates in recent years, focusing on design strategies, diversified material selections and emerging functional applications (Figure 1). We first briefly describe the enhancement mechanisms of SERS substrates to provide insight into the physical origin of their ultra-high, ultra-fast detection ability. Construction methods of flexible SERS substrates, including bottom-up strategies such as interface self-assembly, one-pot method and template assisted method, and top-down strategies of e-beam lithography, nanosphere lithography, optical lithography, holographic lithography, nanoimprint lithography are summarized. This review then moves to diversity material selections of flexible SERS substrates, from metal-organic frameworks, polymer films (polystyrene, polydimethylsiloxane, polymethylmethacrylate, polyethylene terephthalate), cellulose fibers (paper, cellulose, biomimetic material/biomimicked structured), to inorganic materials (semiconductor material, carbon-based nanomaterials). The discussion of various interdisciplinary applications related to food safety, biosensor, medical diagnostics, environmental pollutant detection, and cell culture are further reviewed. The key challenges, prospective directions, and new opportunities of this growing field are finally outlined.

Principles of SERS substrates

Electromagnetic enhancement mechanism

There are two types of SERS mechanisms generally recognized by the academic community: electromagnetic (EM) enhancement mechanism and chemical enhancement (CM) mechanism. For the EM enhancement mechanism, the localized electromagnetic field enhancement caused by surface plasmon resonance (SPR), also called "hot spots" by scholars is considered to be the most important contribution. The free electrons in metal oscillate collectively (which can be regarded as electromagnetic waves) under the action of excitation light, the electromagnetic waves are coupled with free electrons on metal surface, resulting in SPR propagating along the metal surface (Ding et al. 2017). If this electromagnetic field is localized to a small extent on the metal surface, it is called localized surface plasmon resonance (LSPR), which could enhance the Raman signal of the metal nanomaterial surface or nearby molecules by a factor of 10^3–10^8 (Lee, Lee, et al. 2019).The schematic diagram of EM enhancement is shown in Figure 2A. The electromagnetic field in the nanoscale region near the nanostructure is enhanced significantly, while decays exponentially with increasing distance from the surface. This enhanced electromagnetic field promotes the Raman scattering process of molecules near the nanostructures, which is typically called surface enhanced Raman scattering (Su et al. 2021).

Under certain incident light irradiation, a single nanoparticle in the metal plasmonic array structure usually supports the LSPR mode. If it is a uniform spherical metal nanoparticle (<100 nm), the extinction including the scattering cross-section (*Cs*) and the absorption cross-section (*Ca*) can be expressed as (Yang, Pan, et al. 2021):

$$Cs = \frac{8\pi}{3} k^4 a^6 \left| \frac{\varepsilon_m - \varepsilon_d}{\varepsilon_m + 2\varepsilon_d} \right|^2 \tag{1}$$

$$Ca = 4\pi k a^3 \; Im\left(\frac{\varepsilon_m - \varepsilon_d}{\varepsilon_m + 2\varepsilon_d} \right) \tag{2}$$

where k, a, ε_m and ε_d are the wave-vector of incident light, radius and dielectric function of the nanoparticle, and

Figure 1. Overview of flexible surface-enhanced Raman scatting (SERS) substrates.

dielectric constant of the surrounding environment, respectively. It is clear that when $|\varepsilon_m + 2\varepsilon_d|$ is minimum, *Ca* and *Cs* reach the maximum, which contribute to sharp absorption and scattering peaks in the LSPR spectrum. Thereafter, by choosing a suitable excitation wavelength close to the resonance peak of the LSPR, an efficient SPR scattering process can be achieved. For example, Ag nanowafers have better EM enhancement than that of the spherical Ag nanoparticles (AgNPs) at an excitation wavelength of 785 nm (Geng et al. 2018). Under excitation of 636 nm, the Raman peaks of cobalt phthalocyanine (CoPc) on gold films are mainly enhanced by resonance excitation, high EM, and a small fraction of CM (charge transfer from metal to molecule). However, under excitation at 532 nm, the SERS spectrum is dominated by photoluminescence, which is a photo-induced charge transfer process (Chen, Ying, et al. 2019). Furthermore, localized surface plasmons can also be excited by local oscillatory sources (such as dipoles or quadrupoles, etc.) and directionally reradiated to the far field (Ding et al. 2016).

The morphology, size, roughness of the surface metal, as well as the dielectric constant of the surrounding environment play an important role in affecting or controlling the signal strength. Compared with dense gold film, the nanoporous gold film has higher SPR sensitivity and stronger SERS signal (Chen, Liu, et al. 2021). Gu et al. utilized LSPR to generate strong EM at the edges and center of nanowells, enhancing the Ag surface electric field by a factor of 300 (Gu et al. 2013). Since EM enhancement is extremely sensitive to interparticle spacing, a single nanoscale crevice or protrusion may dominate the SERS enhancement over the entire detected area. Tong et al. investigated the SERS-active substrates developed by the structure of single Au nanoparticles(Au NPs), showing that the closest distance difference of one or two nanometers may lead to significant changes in EM (Tong, Zhu, and Liu 2011).

Kumar et al. reported direct experimental evidence that the EM mechanism of SERS is a dual phenomenon of simultaneous enhancement of incident excitation and scattered

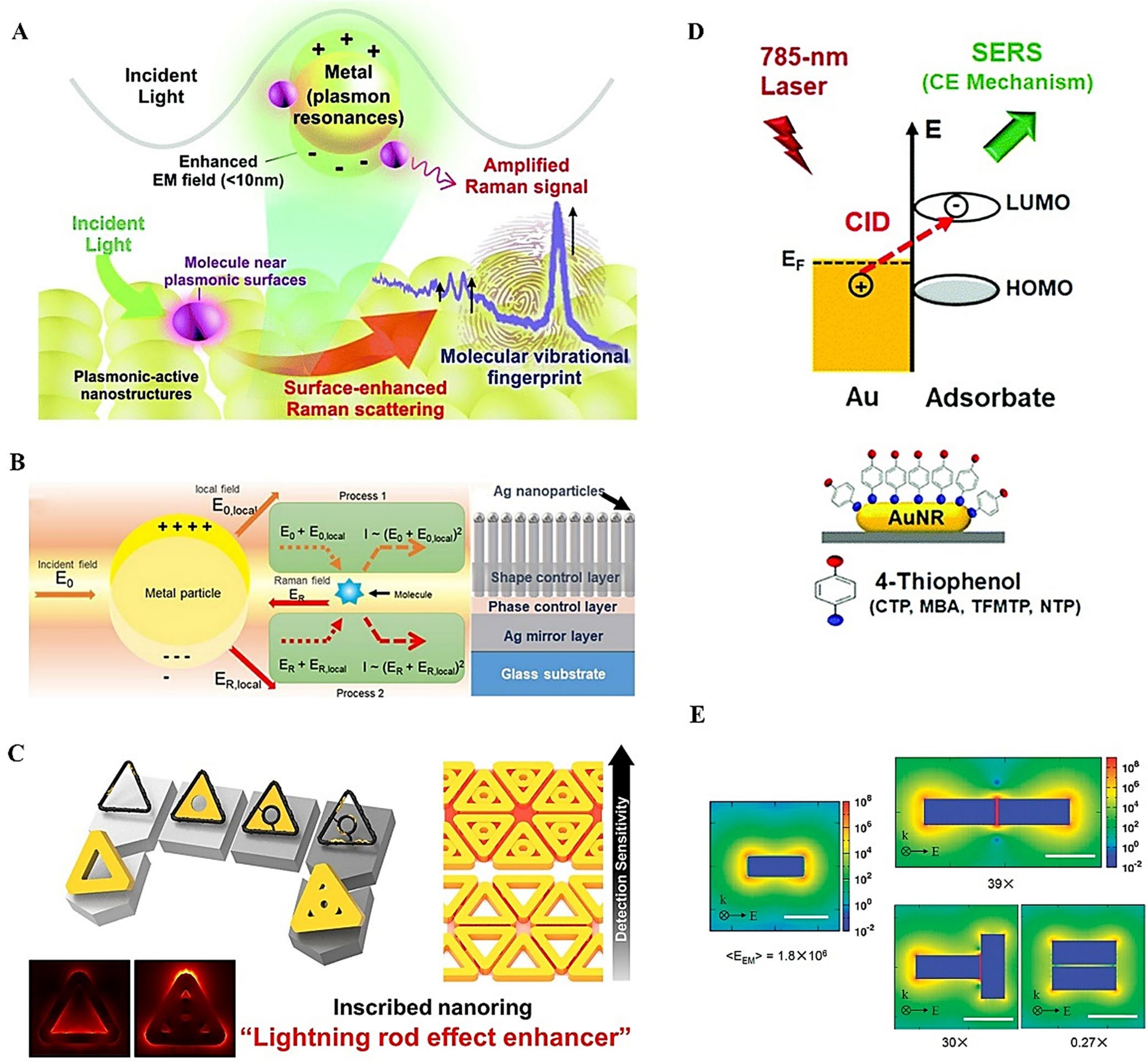

Figure 2. A) Schematic representation of the surface of noble metal structures supporting localized surface plasmon resonances (LSPRs) for SERS enhancement. Reproduced with permission (Lee, Lee, et al. 2019). Copyright 2019, Royal Society of Chemistry. B) Schematic diagram of dual EM SERS enhancement and multilayer thin film "localized plasmon resonator." Reproduced with permission (Kumar et al. 2020). Copyright 2020, American Chemical Society. C) Schematic diagram of synthesis of angular nanoboxes (TNs) and electric field enhanced contour map of AuTNs. Reproduced with permission (Go et al. 2022). Copyright 2022, American Chemical Society. D) Schematic diagram of chemical interface damping (CID) mechanism with CM in SERS. Reproduced with permission (Seo et al. 2020). Copyright 2020, Royal Society of Chemistry. E) The mechanism underlying CM between p-aminothiophenol (PATP) and the Ag/MoO_3 composites. Reproduced under terms of the CC-BY license (Chu et al. 2021). Copyright 2021, the Author's. Published by MDPI.

Raman fields, the schematic illustration is shown in Figure 2B, which is called the AgNRAs(Ag nanorod arrays)/SiO_2/Ag mirror multilayer thin film "localized plasmon resonator" (Kumar et al. 2020). The optical properties of these fabricated plasmonic-photonic microspheres (PPMs) could be tuned by varying the sizes of the building blocks and the nanogaps between adjacent gold nanocrystals. Finally, the synergy of photon blocking band (PSB) and LSPR is realized, and the enhancement factor (EF) of the obtained SERS is as high as 10^8 (Wang, Le-The, et al. 2020). It is evident from the study by McMahon et al. that rod-shaped and triangular-shaped particles have the highest mean EF among isolated particles, and particles with sharp tips or edges have higher EF than those without. Due to the destructive interference between symmetrical dipoles induced in each particle, the side-by-side rod dimers do not show obvious hot spots between particles, indicating that the existence of only gaps does not guarantee high enhancement effect (McMahon et al. 2012). However, this phenomenon is not common as this particular form of symmetry is difficult to produce in practice. In general, the local field varies with nanoparticle structure and gap size. It is demonstrated that $|E|^2$ (where E is the enhancement of the electric field) varies inversely with increasing gap, while the electromagnetic SERS EF versus gap (size) is approximately $1/gap^2$ for the optimally selected particles.

Another mechanism of EM is the tip effect, which causes the dipole fields of particles to concentrate near their tips, owing to the concomitant enhancement of electric field lines crowding near sharp metallic features. The greatly enhanced near field makes plasmonic nanoparticles widely used in SERS (Yang, Pan, et al. 2021). To take advantage of the tip effect to obtain large EFs and ensure high reproducibility for active SERS substrates, Cialla's team prepared plasmon arrays composed of sharp-edged nanostructures instead of the commonly used spherical or dots (Cialla et al. 2008). Au nanostar (AuNS) arrays could be obtained by one-step method and Au nanodiamond (AuND) arrays are realized by two-step method. By comparison, it is found that the EF of AuNS arrays is more than twice that of AuND arrays (Cialla et al. 2008). Lin et al. studied the active substrate prepared by hexagonal Au nanorods, changed the "ring diameter" (Dr) produced by the convergence of three hexagonal nanorods, and optimized the ratio of Dr/Dt (the diameter of the target virus) (Lin et al. 2012). It is found that when the ratio is 1, the recognition ability of the virus and the SERS mechanism are obvious, and the researchers explain that it may be caused by the tip effect around Dt.

Nanoparticles of different sizes with the same morphology also affect the enhancement. Lin's research group synthesized gold nanorods of various sizes but supported the same LSPR wavelength, kept the LSPR of the nanorods unchanged, and studied the size dependence of the nanorods (Lin et al. 2016). The stronger SERS signal at the smaller size is due to the synergy of stronger tip effect and weaker radiation damping, resulting in stronger local field enhancement. Lee et al. outlined five main approaches to enhance SERS performance, which could be combined with engineering hot spots to further improve SERS sensitivity that cannot be achieved with hotspot engineering alone (Lee, Lee, et al. 2019). The constructed AuNS@4-MBA@Au structure provides a higher EF of SERS thanks to the favorable electromagnetic field between the AuNS core and the Au shell, and thus the AuNS exhibits greater surface roughness and tip effect, resulting in a super strong SERS signal, enabling detection limits as low as 0.25 fg mL^{-1} for ochratoxin A (OTA) (Huang, Li, et al. 2020).

Go et al. synthesized Au ring-triangular nanoframes with high structural stability. The presence of inscribed nanorings plays an important role in the tip effect, and the EM near-field enhancement occurs on the highly curved curvature of the metal interface (Figure 2C) (Go et al. 2022). Recently, based on the tip effect of Au pine needles with a large number of sharp corners and edges under an external magnetic field, some scholars have completed the electrochemical-LSPR-driven hydrogenation of 4-NTP to 4-ATP in aqueous solution, showing excellent catalysis (Tian et al. 2022). This opens up a new avenue for promoting direct plasmonics-driven hydrogenation reactions.

Chemical enhancement mechanism

Chemical enhancement (CM) mechanism, which refers to chemical interaction between the metal substrate and Raman reporters adsorbed on its surface, resulting in the formation of a new charge-transfer excited state in the complex system. Under the incident photo-field, an electron can jump from the metal energy level to the molecular excited state orbitals or from the molecular orbitals to the metal unoccupied energy level. If the energy of incident photon matches that of the charge-transfer leap, a charge-transfer leap resonance is generated, which increases the effective polarizability of the molecule and leads to an increase in the Raman scattering cross-section, resulting in an enhancement of the Raman signal, typically by 1–3 orders of magnitude. The change in the molecular magnetization rate leads to a change in the CM effect, the mechanism of which is usually explained by density functional theory (DFT) simulations. In addition, the magnitude of the charge transfer enhancement is related to the nature of the electronic structure of the probe molecule and substrate. Goul et al. found that the graphene weakened the electric field on the surface when graphene or Rhodamine 6 G (R6G) was between two nanoparticles. Despite the dampened electric field, the synergistic effect of graphene and Ag nanoparticles (AgNPs) resulted in a greater enhancement of the Raman signature of R6G compared to graphene or nanoparticles alone, which was attributed to the charge transfer (CT) mechanism effect of graphene. And the detection sensitivity of R6G was able to reach 8×10^{-7} M (Goul et al. 2017).

Sinthiptharakoon et al. investigated the local electronic properties of the semicontinuous Au film-based SERS substrates by means of conductive atomic force microscopy and Kelvin probe force microscopy (Sinthiptharakoon et al. 2018). This study showed that SERS enhancement is attributed to a two-step photoinduced CT in which free electrons from the supportive layer of the SERS substrate play a dominant role. In recent years, SERS substrates prepared from semiconductor materials such as graphene, some inorganic compounds and organic compounds can also generate strong SPR owing to CT effect (Wang, Zhu, et al. 2017). The experimental and theoretical results of Tian et al. demonstrated that the SERS activity of VO_2 nanosheets is comparable to that of noble metals, mainly due to the strong SPR effect and strong interfacial interactions based on CT effect (Tian, Zhang, et al. 2019). The high EF exhibited by graphene on SERS-active substrates is also derived from the CM mechanism. Based on density functional theory (DFT), Prasad et al. showed that CT effect occurs in the rippled graphene, the increase in the polarizability and anisotropy of the substrate leads to a 1000-fold increase in the EF (Prasad et al. 2020).

Chemically doped graphene may shift the Fermi level and even enhance charge transfer when the shift is aligned with the molecular LUMO, thereby significantly amplifying the Raman molecular vibrational modes (Feng et al. 2016). Seo et al. found that in SERS, chemical interfacial damping (CID) is closely related to CM, as illustrated by Figure 2D, thus CM can be promoted by tuning CID in AuNPs under resonance conditions while maintaining high SERS intensity (Seo et al. 2020). Chu and coworkers co-sputtered Ag/MoO_3 composite system on polystyrene (PS) colloidal microsphere array by Argon plasmonics bombardment method. The MoO_3-rich oxygen vacancy defect generated by this method compensates for the wide band gap of MoO_3 and provide a channel for CT in this system (Figure 2E). This interesting phenomenon opens up new horizons for the study of oxygen-containing semiconductors in SERS substrates (Chu et al. 2021). Nowadays, a growing number of scholars are beginning to pay attention to the SPR changes of metal-semiconductor composites, which will help further study of interfacial charge transfer (Ma et al. 2019; Han et al. 2020).

Design strategies for flexible SERS substrates

Bottom-up methods

The bottom-up method refers to the self-assembly of some small structural units (such as atoms, molecules, nanoparticles, etc.) into relatively large structures (or assemblies) with stable, special properties, and complex micro/nano structural systems through weak interactions, which include the gravity, stress, centrifugal force, electrostatic interactions (Zhu et al. 2020), hydrogen bonds, coordination bonds, π-π interactions (Ma and Yung 2016), capillary forces, hydrophilic or hydrophobic. Self-assembly technology has the advantages of easy operation, low cost, large-area order and easy control, which has attracted extensive attention in recent years. According to the assemblies and related refinement technologies, the self-assembly methods have also formed strategies such as interface self-assembly, template-assisted approach, colloidal deposition, one-pot formation, magnetron sputtering method, anodic oxidization, electrophoresis-assisted sedimentation method. This sub-section mainly reviews three typical and commonly used self-assembly strategies, namely interface self-assembly, one-pot method and template-assisted approach, for more summary of construction methods, please refer to Refs. (Ye et al. 2021; Shiohara, Wang, and Liz-Marzán 2014).

Interface self-assembly

Interface self-assembly has the merits of simple, versatile, fast and inexpensive, compared with other substrate fabrication approaches. Guo et al. developed a facial method for self-assembly of gold nanoparticle monolayer films at the air/water interface, which is characterized by tight packing, large size, and high uniformity. It can be transferred to rigid substrates and used as active SERS substrates with high stability (Guo et al. 2016). Ma and collaborators proposed a new strategy to self-assemble gold nanoplates into three-dimensional hierarchical gold nanoflowers (AuNFs) via π-π stacking and interfacial reduction reactions (Ma and Yung 2016). The AuNSs were assembled at the water-hexane interface, and abundant nanogaps could be formed in the prepared monolayer AuNS films because of the electrostatic repulsion and Van der Waals forces between the tips of the nanostars (Cong et al. 2021).

Lu et al. reported a strategy of using chemical crosslinking at the air-water interface to realize large-scale single-layer Au nanoparticle (AuNP) film (Figure 3A). The film has intelligent and adjustable nanogaps, which can amplify SERS signal to the greatest extent (Lu et al. 2018). The unique Au superparticles (AuSPs) are confirmed theoretically and experimentally with high stability, uniform morphology, and multiple notches, forming densely distributed hot spots, making them reliable SERS substrates. Therefore, the self-assembled AuSPs can be used as SERS substrates to simultaneously achieve in-situ extraction for on-site quantitative determination of organochlorine pesticides in environmental water (Li, Chen, et al. 2021). Yang et al. innovatively obtained a three-phase self-assembly method, the spontaneous transfer of AuNPs from the water/organic interface to the water/air interface (Figure 3B), and finally formed a monolayer of AuNPs with local hexagonal close packing (Yang, Nanda, et al. 2017). Adding n-hexane to gold colloids via vortex mixing, without involving organic additives, prepared SERS substrates formed at the water/oil interface in a simple and time-consuming manner (Teng et al. 2019).

In SERS technology, the high efficiency and long-term storage stability of plasmonic substrates are crucial for practical applications in practical analysis, and the ternary thin film encapsulation of silver nano-gold (Au@Ag-NP) SERS chips can achieve high performance and long-term storage stability at room temperature (Wang, Sun, et al. 2019). Ye et al. summarized the recent status of self-assembly of colloidal nanoparticles into two-dimensional arrays at the water-oil interface, offering guidance for rational construction of active substrates (Ye et al. 2021). In short, great progress has been made in the method of interfacial assembly of nanoparticles. According to the properties of nanomaterials and interfacial liquid or gas, it is our constant pursuit to select an appropriate method to prepare a satisfactory substrate.

Besides, for magnetic materials, it is very necessary to adjust the magnetic anisotropy of magnetic nanoparticles (MNP) in controlling SERS signal strength and detection sensitivity. Wen et al. demonstrated that the magnetocrystalline and magnetic shape anisotropy of hierarchical MNP assemblies can be controlled to obtain self-assembled nanoplates with excellent properties (Wen et al. 2017). The kinetic principle of two-step assembly of AuNPs was studied by Lyu et al., contributing to the future research on the mechanism of self-assembly of metal nanomaterials (Lyu et al. 2021). Recently, some scholars had also prepared SERS substrates by inkjet printing of aqueous emulsions containing metal and polymer colloidal nanoparticles, and this method can be very simple to construct SERS substrates (Martins et al. 2021; Fernandes et al. 2022). The SERS sensor was constructed based on the dense monolayer of self-assembled Au nanocubes (AuNCs), which could detect 5-thio-2-nitrobenzoic acid (TNB) molecules formed by the cleavage of disulfide bonds in 5,5′-Dithiobis-(2-nitrobenzoic acid) (DTNB) (Li, Chen, et al. 2021). Because there is a good linear relationship between the relative spectral intensity of TNB characteristic peaks and the concentration of

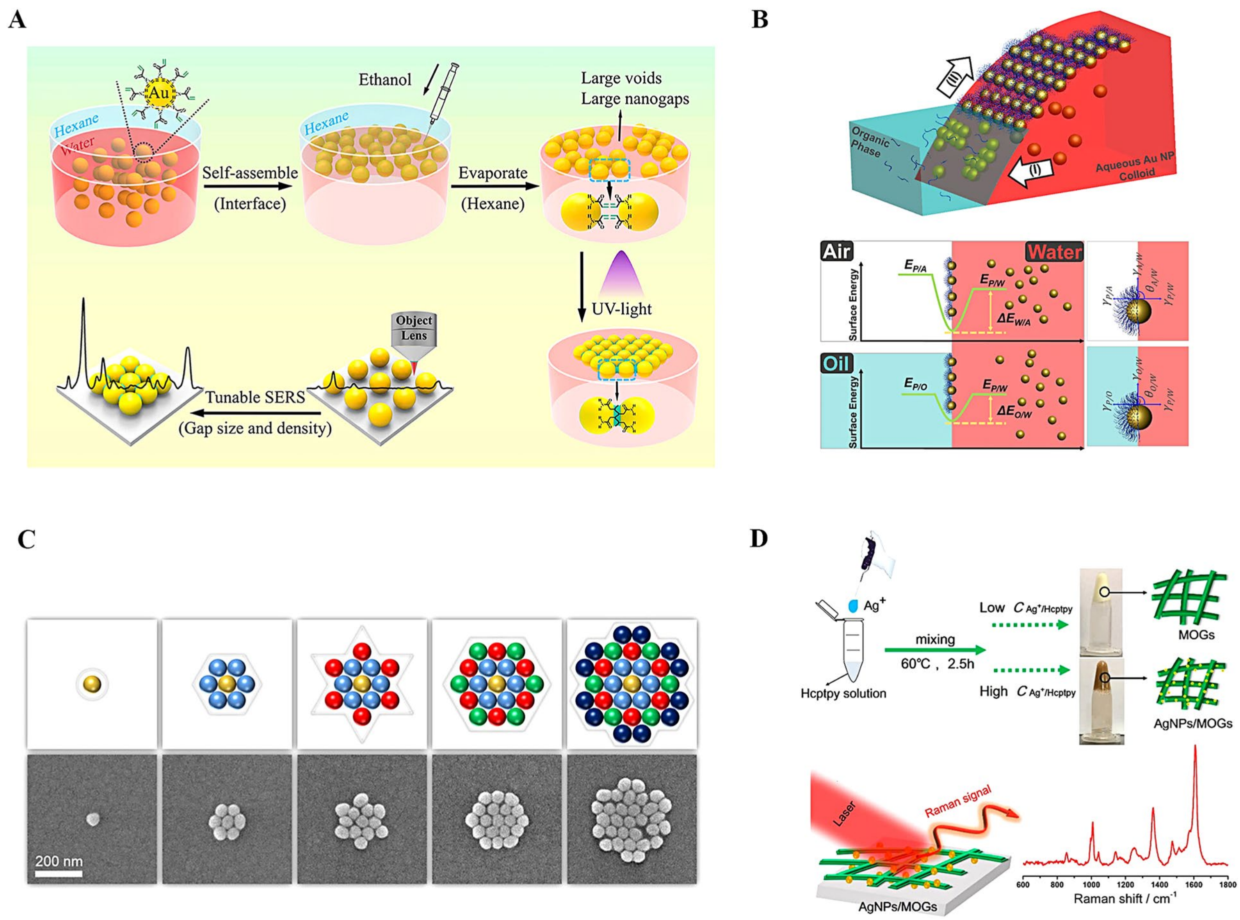

Figure 3. Schematic illustration of the bottom-up fabrication strategy. A) Assembled at the air-water interface to form AuNP monolayers. Reproduced with permission (Lu et al. 2018). Copyright 2018, American Chemical Society. B) Assembly of AuNP monolayers using a three-item system of water, oil, and air. Reproduced with permission (Yang, Nanda, et al. 2017). Copyright 2017, American Chemical Society. C) Template-assisted self-assembly to form Au nanocrystals. Reproduced with permission (Greybush et al. 2017). Copyright 2017, American Chemical Society. D) One-pot development of AgNPs/MOGs hybrids. Reproduced with permission (Li, Heng, et al. 2019). Copyright 2019, American Chemical Society.

glutathione (GSH) in a certain wavelength range (Li, Chen, et al. 2021), it has important guiding significance for the detection of clinical medicine.

One-pot method

The one-pot method can directly obtain molecules or complexes with complex structures from relatively simple and readily available raw materials without separating intermediates, which is economically and environmentally friendly. 3-aminophenylboronic acid (APBA) reduces $HAuCl_4$ to small AuNPs, which self-assemble into gold superparticles (AuSPs) by a simple one-pot method via π-π stacking of the oxidation products of APBA. Then, AuSPs were used as highly sensitive and multi-band SERS nanotags (Ma, Promthaveepong, and Li 2017). The direct synthesis of high-quality hyperbranched Au dendrites by a cost-effective one-pot method using PVEIB as structure directing agent and stabilizer has great potential for in situ detection and analysis of trace analysis such as food contaminants (Feng et al. 2017). Kim et al. designed a novel paper-based 3D SERS substrate and established a convenient one-pot gold electrodeposition method for the direct detection of the concentration of pyocyanin secreted from the medium during bacterial culture (Kim et al. 2022). This is very meaningful for early diagnosis and treatment.

Magnetic composites could also be prepared by a one-pot method (Yang, Nanda, et al. 2017), which can be applied for adsorption removal and degradation of organic pollutants and detection. In addition, 2D gold nanoplates (2D AuNPLs) were synthesized in one-pot on carbon nanotube (CNT) sheets as supporting materials (Xin et al. 2017). Microspheres with multiple gold nanoparticles embedded in mesoporous silica (AuNPs/$mSiO_2$) was also used as substrates for active SERS substrate (Chen et al. 2017). In recent years, metal-organic gels (MOGs) have emerged as a potential substitute for metal-organic frameworks owing to their unique properties. Green AgNPs/MOGs have been created with simple preparation process and good enhancement effect, which can be used as bifunctional SERS platform (Figure 3D) (Li, Heng, et al. 2019). Wang et al. synthesized hyaluronic acid-coated gold nanoparticles (HA-AuNPs) by a one-pot method, used malachite green (MG) as a Raman probe to measure hyaluronidase (HAase), and described the detection in detail in their paper mechanism (Wang, Le-The, et al. 2020). Moreover, compared with other HAase assay methods, this method is more efficient and convenient. Li et al. used a one-pot synthesis of nanosilver and molybdenum disulfide nanocomposites as inks to fabricate a large number of wearable SERS array sensors on flame-retardant fiber gloves by screen printing (Liu, Zhao, et al. 2022).

Template-assisted approach

With the help of the template, the particles can form a self-assembled structure in a specific way, so that the final assembly can form an ideal one-dimensional, two-dimensional or three-dimensional (3D) array in space. Greybush et al. studied the assembly of 1–31 members of hexagonally ordered gold nanocrystal oligomers into polygonal topographic templates by capillary force with the help of templates, and the size-dependent spectral features were confirmed by simulation. The contributions of magnetic dipole, electric dipole and Fano resonance modes to the scattering spectrum are also elucidated (Figure 3C) (Greybush et al. 2017). Matricardi et al. assembled the SERS substrate with the aid of PDMS template-assisted gold nanospheres and found that a 785 nm laser is the optimal configuration for this substrate (Matricardi et al. 2018).

Similarly, Garg et al. used capillary forces to drive the self-assembly process of micropatch arrays generating AuNP aggregates within a hydrophobic microstructure template (Garg, Nam, and Zhou 2020). Then through the nanoimprint technology we will talk about later to make it tightly bonded to the polymer to form a stretchable substrate. Jia et al. deposited nanoparticles directly on the template and then used tape transfer, revealing different plasmonic modes for strain sensing, providing a new direction for the development of new plasmonic technologies (Jia, Kong, and Ebendorff-Heidepriem 2020). Templates for strips of filling material were prepared in advance by Korkmaz et al. The diatom-AgNP SERS substrates were then prepared using two different methods. The first method is to obtain pure diatom strips on scotch tape by template and drop different volumes of AgNP suspensions. The second method is to prepare diatom-AgNP composites with different AgNP concentrations, then dry them using a template and prepare into strips affixed to adhesive tapes (Korkmaz et al. 2018). Both methods are flexible, robust, inexpensive, and their simplicity makes them widely available.

Template-assisted colloidal self-assembly of spherical AuNPs was also used to prepare highly regular supercrystal arrays by Charconnet et al. (2021). A drop of colloidal dispersion of monodisperse Au nanospheres was stabilized with polyethylene glycol (PEG) and dried under a template mold made of polydimethylsiloxane (PDMS). The pre-patterned template was scaled to a period of 500 nm in a square lattice using circular holes containing a diameter of 270 nm and a depth of 87 nm. The resulting plasmonic superlattice consists of clusters, also known as densely filled supercrystal substructures, in a regular ordered arrangement allowing strong far-field coupling (Charconnet et al. 2021).

Sandpaper has a very rough surface, which is cheap and durable, and can be used as a potential template. Sun et al. formed a sandpaper molded PDMS-SERS substrate with a rough and uniform surface over a large area, and also maintained sensitivity and stability, which makes the substrate prepared by this method splendid commercial prospects. The mechanical strength and ductility of PDMS were verified in deformation experiments, and its mechanical properties were found to meet specific application requirements (Sun et al. 2019). In addition, anodized aluminum oxide (AAO) (Liao, Liu, et al. 2021; Muhammad, Shao, and Huang 2021; Wang, Xu, et al. 2022; Xiang et al. 2022), as a porous material with good mechanical strength and thermal stability, is also commonly used for the template-assisted formation of SERS-active substrates.

Top-down lithography

The top-down method generally refers to the preparation of the desired nanostructures by various etching techniques from substances of large size (from micrometers to centimeters). The advantage is that it can easily prepare various exotic and uniform 3D structures on a large scale, it can also prepare porous materials that inherit the original morphology and structure. Nevertheless, the disadvantage is that the technology has high requirements on experimental instruments and laboratory personnel, high cost, and large consumption of experimental materials. When large-sized materials are etched into small-sized nanomaterials, the remaining materials are wasted. Meanwhile, the microscopic morphology of the target material is limited, and the morphology cannot be adjusted by controlling the distance between atoms or ions once it is fabricated. Common top-down techniques include e-beam lithography (EBL), nanosphere lithography (NSL), optical lithography (OL), holographic lithography (HL), nanoimprint lithography (NIL) or chemical etching to create nanostructures on the surface, followed by metal deposition nanolayers.

Notably, most of these technologies require expensive facilities, complex operations, and high technical requirements, among which nanoimprinting technology may be used relatively more. Park et al. constructed SERS substrates by reactive ion etching to obtain polymer nanopillars with a width of tens of nanometers, and the nanogap would generate a stronger signal (Park et al. 2019). The ordered 3D probe structure was fabricated directly on the fiber end face via reactive ion etching (RIE) method (Meng, Shang, et al. 2022). The SERS active surface area is guaranteed, and the stability of the probe is also improved. The 3D SERS probe exhibits the characteristics of high sensitivity, low cost, good stability, and miniaturization. Gimenez et al. fabricated tunable periodic nanocavity arrays by oxygen plasmonics etching technology, which can not only construct a single substrate, but also replicate the construction of multiple arrays (Gimenez, Kho, and Keyes 2020).

Although high-performance SERS substrates are obtained with these sophisticated nanofabrication techniques, generating nanoscale features often requires a photoresist liftoff process, which is time-consuming and challenging for large-area production. Chang et al. simplified the e-beam lithography technique and realized the large-area preparation of SERS-active substrates in a short time, which possess the features of highly uniform and reproducible (Chang, Huang, and Lin 2020). The Cu nanoparticles produced by chemical etching by Sajitha et al. had uniform nanopore morphology and enhanced SERS activity by a factor of about 10 (Sajitha et al. 2021). The subsequent galvanic displacement reaction led to Ag nanoflower growth, showing multimodal plasmonic absorption. The excellent uniformity and simplicity of the procedure, coupled with the ultra-sensitivity, make it possible to fabricate high-quality SERS-active substrates with minimal investment (Sajitha et al. 2021).

It can be seen from Figure 4A that flexible SERS substrates across the entire wafer size are achieved by one-step metal-assisted chemical etching (Lu et al. 2022). The pre-patterned Si wafers allow porous silicon (PSi) structures to form in regions of several 10 microns, thus allowing PSi thin film sheets to be easily separated from the bulk Si substrate. The PSi film morphology, pore size and porosity can be precisely controlled by varying the etchant concentration, which has a pronounced effect on film wettability and integrity. Both rigid and flexible PSi films before and after the transfer exhibited significant SERS effects. In addition, flexible substrates have been shown to be highly sensitive (up to 2.6×10^{-9} g/cm^2) when they are used to examine methyl parathion residues on curved apple surfaces (Lu et al. 2022).

The arrayed nanostructures are simply fabricated on plastic films using NIL. Cai et al. fabricated highly ordered noble metal NPs on flexible substrates using easy-to-control NIL and plasmonics sputtering techniques (Figure 4B). The EF value of the SERS substrate is 0.8×10^{11}, the RSD is as low as 3.72%, and the overall performance is relatively good (Cai et al. 2021). NIL generated uniform periodic nanohole patterns (NHPs) across the substrate and applied high potentials to create high-density arrays of silver nanostructures within each hole pattern. The active SERS substrate exhibit 10^{10} signal enhancement and good reproducibility (Lee, Lee, et al. 2019). Kudilatt et al. combined two lithography techniques to construct the flexible SERS substrate (Hasna et al. 2016). The Si master with triangular pits is firstly obtained by electron beam lithography, and then the PMMA is formed into a triangular column array by nanoimprinting technology. Finally, the AgNPs are deposited on the flexible polymer. Ultrasensitive SERS substrates are generated. A high-sensitivity SERS active substrate with reproducibility, large-area uniformity, and an EF of 2.9×10^{11} was fabricated by nano-triangular-pillar arrays.

Several different hybrid nanostructures were investigated and compared by measuring the EF and surface plasmon resonance thickness sensitivity using hot pressing NIL to simply fabricate well-aligned and cost-effective nanostructures into plastic films. It was evaluated which nanorod and nanowire composites have outstanding SERS performance (Lee, Hung, et al. 2018). The preparation process of gold nanostructures is depicted in Figure 4C (Lee, Hung, et al. 2018). Besides, microporous multi-resonant plasmonic mesh devices were constructed by hierarchical micro/nanoimprinting of dissolvable polymer templates (Garg et al. 2022). It can be used as bio-interface sensing for long-term disease diagnosis. Colniţa et al. fabricated nanotrenches in plastics using NIL and covered them with nanostructured Ag films

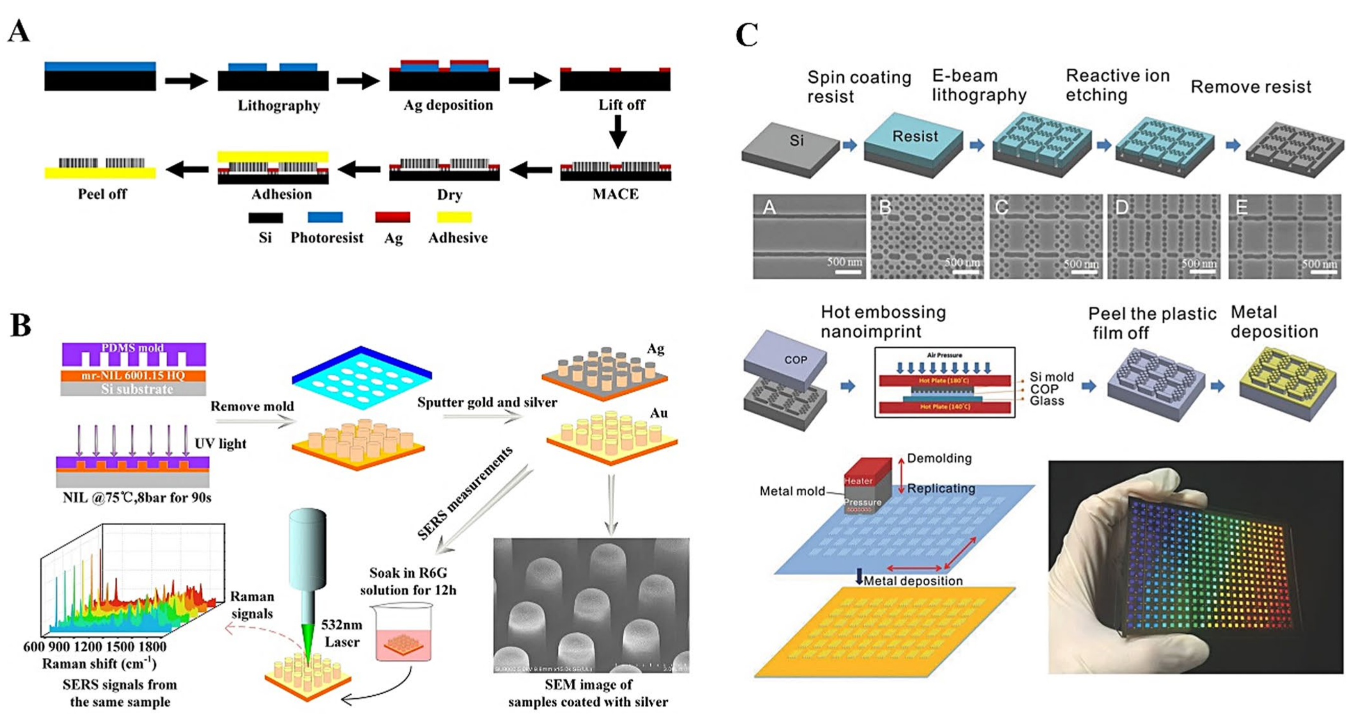

Figure 4. Schematic representation of the top-down preparation strategy. A) Porous silicon obtained by metal-assisted chemical etching. Reproduced under terms of the CC-BY license (Lu et al. 2022). Copyright 2021, the Author's. Published by MDPI. B) Highly ordered noble metal NPs were fabricated on flexible substrates with NIL. Reproduced with permission (Cai et al. 2021). Copyright 2021, Elsevier B.V. C) Fabrication of metal nanostructures using etching and nanoimprinting techniques. Reproduced with permission (Lee, Hung, et al. 2018). Copyright 2018, John Wiley and Sons.

with thicknesses in the range of 10–100 nm deposited by DC sputtering (Colniță et al. 2022). The silver film thickness can be increased by successive deposition times and its contribution to the obtained EF is determined. It is found that the SERS signal is significant enhanced when the Ag film is selected as 25 nm. Compared with other thicknesses of metal films, this substrate has a lower SERS detection limit of 10 pM, with better uniformity and signal reproducibility (Colniță et al. 2022).

Material selections of flexible SERS substrates

Metal nanomaterials

Noble metals

The interaction of electromagnetic fields with the nanoparticles affects their optical properties, which are mainly determined by the dielectric constant of the material at the excitation wavelength and the surrounding medium. The plasmonic noble metal materials (mainly Au and Ag) exhibits highly SERS-enhancing because of their unique SPR properties in the visible region, while the materials such as aluminum (Al), titanium (Ti), gallium (Ga), and platinum (Pt) exhibit the plasmonic resonance in the deep ultraviolet (UV) region (Rajesh et al. 2021; Bharati and Soma 2021). The SPR performance also depends on the shape, size, arrangement and morphology of the metal nanostructures (Cao et al. 2015). Therefore, the key to a wider application of SERS technology in terms of substrate preparation materials is to develop plasmon-resonant structures with novel geometries to enhance the Raman signal and to control the periodic order of these structures over large areas to obtain reproducible Raman enhancement (Cao et al. 2015). The Raman signal enhancement comes from a number of specific sites that are known as hot spots. The spectral signal of the detected substance (or Raman molecule) in this region will be significantly enhanced, which is the desired characteristic. Therefore, metal nanomaterials play a very important role in the preparation of SERS substrates.

To obtain significant SERS signals, some necessary construction techniques (or systems) are typically utilized to modify and change the volume, shape or edge curvature of metal nanomaterials for the design of specific hot spots. In the essence of constructing SERS substrates, metal materials are usually essential, the most commonly used metal materials are noble metals such as Au and Ag, both of which are plasmonic materials with excellent performance, of which silver has a high-quality factor but is easily oxidized, while gold has excellent chemical stability. Scholars make them into nanorods (Lin et al. 2016; Tian, Li, et al. 2017), nanocylinders (Safar et al. 2020), nanocubes (Omar et al. 2017; Wang, Sun, and Li 2015), nanospheres, nanowires (Zhai et al. 2019), nanostars (Huang, Li, et al. 2020), Au nanobipyramids (Zhao et al. 2021), nanoflowers (Sajitha et al. 2021) and other shapes to enhance the interaction between particles, produce obvious SERS signals.

By using thiol molecules to engineer targeted surface functions, Yang et al. achieved the control over the geometry and spatial orientation of AgNCs in assembled metacrystals, breaking the current configuration of nanocubes that are confined to plane-to-face configurations (Yang et al. 2016). AgNCs can be oriented into planar, tilted, and upright configurations (Figure 5A) and assembled into densely packed square, linear, and hexagonal metacrystals, respectively. Large-area EM field delocalization in nonplanar hexagonal metacrystals produces the strongest EF in SERS among the three metacrystals. When using 4-methylbenzenethiol (4-MBT) as the probe molecule, the EF of this low packing density metacrystal is 1.5×10^6, which is nearly 350 times higher than the SERS enhancement coefficient of the planar square close-packed lattice (Yang et al. 2016).

The 3D dendritic Ag material with high tip effect and accessible surface area constitutes a first-order enhancement for paper-based sensors (Zhao et al. 2020). Molecular markers are coated on the Ag dendrite layer as an intermediate layer for target capture and enrichment. Subsequently, the LSPR of the top layer AgNPs with rough surface forms a secondary amplification enhancement. Splendidly, the superimposed coupling of dendritic 3D Ag with AgNPs electromagnetic fields achieves multi-level enhancement of the SERS signal (Zhao et al. 2020). Using the as-synthesized well-faceted Au nanopolyhedrons (AuNPHs) as the bulk building block, self-supporting AuNPHs superlattice sheets were fabricated through a drying-mediated self-assembly and soft ligand equilibration strategy (Figure 5B) (Chen, Liu, et al. 2021). Li et al. prepared AgNC monolayers by dropping different concentrations of colloids onto Si substrates using the dropping method, and in turn, used the Langmuir-Blodgett technique to further increase the surface coverage of AgNC monolayer substrates (Wang, Sun, and Li 2015). High density AuNP monolayers were also prepared by interface assembly, and its nanogaps can be controlled to sub-1-nm (Si et al. 2016). Tian et al. used a seed mediated method to synthesize silver nanorods. The rod length can reach 5000 nm (Tian, Li, et al. 2017). The formed film has vertical orientation and the longest rod length, which can obtain the best SERS performance.

By depositing AgNPs on an ordered micro-pyramid array, the prepared substrate has high sensitivity, excellent stability, and high reproducibility (Zhang, Chen, et al. 2021). Tong et al. reviewed the preparation methods and applications of silver as a substrate for SERS, and also provided directions for selecting silver as a material for SERS in the future (Tong et al. 2018). Recently, 2D AuNPs monolayers have received increasing attention in multiple disciplines due to their macroscopic size and controllable electromagnetic enhancement, electron transport capability, and unique optical trapping. Song and coworkers overviewed the structure of AuNPs 2D monolayer molecular films, surface engineering strategies, and applications after functionalization in light/electric fields (Song et al. 2022). This review will contribute to a better understanding of 2D AuNPs monolayers, a more systematic understanding and an optimal preparation method in subsequent studies. In the last few decades, metamaterials as a kind of artificial electromagnetic functional materials, their unique properties and revolutionary application prospects have also attracted the attention of countless scholars. A multilayer hyperbolic metamaterial SERS

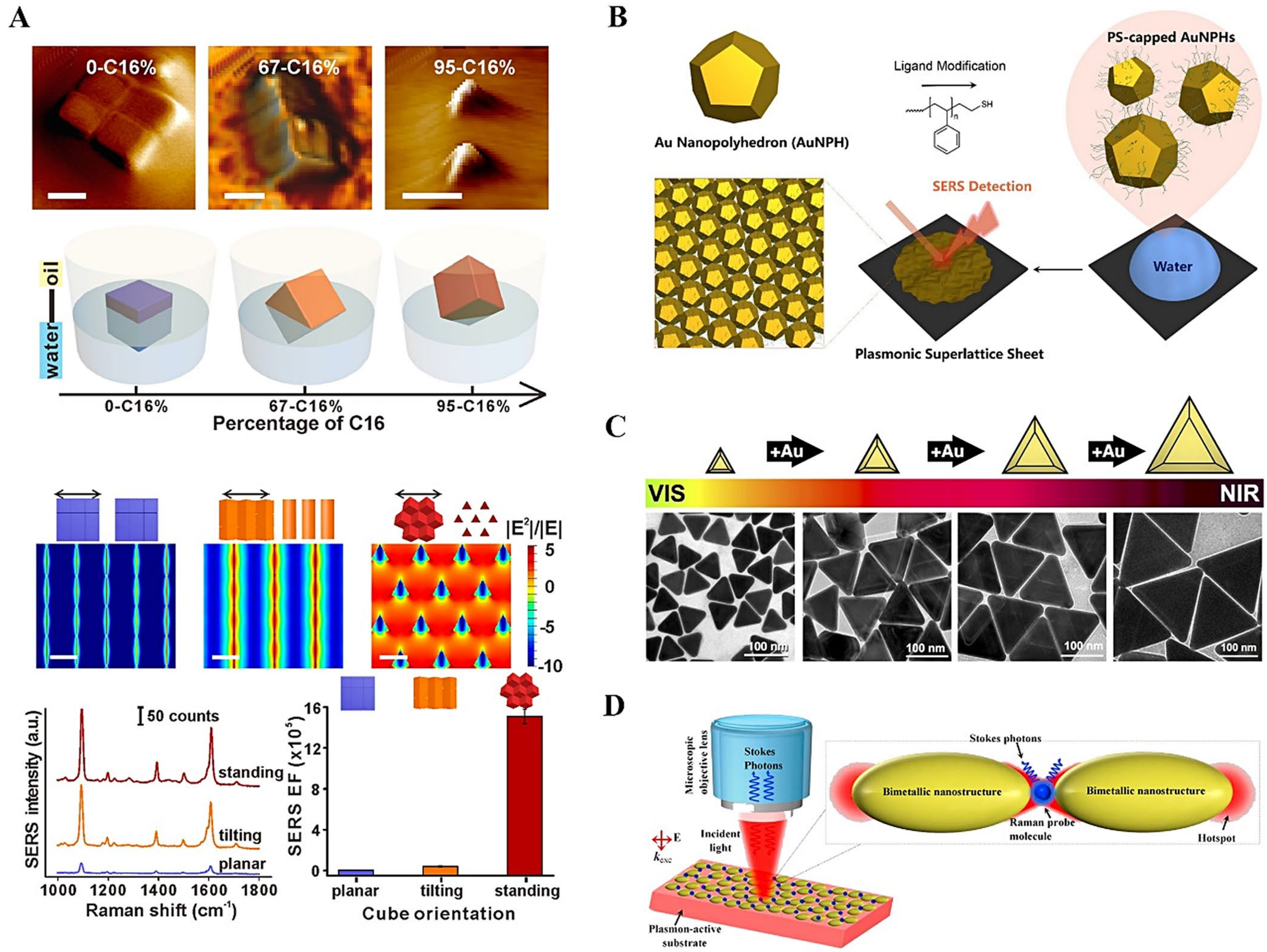

Figure 5. A) Different functionalized AgNCs (planar, tilting, and standing) and controllable sub-crystal structures provide tunable light-matter interactions. Reproduced with permission (Yang et al. 2016). Copyright 2016, American Chemical Society. B) Plasmonic superlattice sheets constructed from AuNPHs. Reproduced with permission (Chen, Liu, et al. 2021). Copyright 2021, American Chemical Society. C) Au nanotriangles. Reproduced with permission (Kuttner et al. 2018). Copyright 2018, American Chemical Society. D) Device for recording SERS spectra using Au-Ag bimetallic prolate spheroid-shaped nanostructures. Reproduced with permission (Das et al. 2021). Copyright 2021, Elsevier B.V.

substrate was fabricated by Shafi et al., including monolayers of AgNPs and Au-Al_2O_3 films (Shafi et al. 2021). The AgNPs layer excites surface plasmon polaritons (SPPs) and bulk plasmon polaritons (BPPs), as well as the LSPR of the AgNPs layers coupled with the BPPs, generating strong electromagnetic fields at the interparticle gaps of the AgNPs. Both simulations and experiments demonstrate that the proposed hyperbolic metamaterial SERS substrate exhibits high homogeneity, good stability, and reproducibility.

Seed-mediated growth is one of the most widely used methods to prepare metal nanomaterials. It can be used to achieve SERS active materials with hollow silica-coated Au shell particles (Zhang, Peng, et al. 2020). Kuttner et al. demonstrated the synthesis of gold nanotriangles (AuNTs) using 3-butyric acid in the presence of benzyldimethylammonium chloride as the capping agent. The particle size and shape are then controlled by studying three parameters, temperature, solution pH, and reducing agent concentration. Then, the size of AuNTs was increased by seed-mediated overgrowth of Au (Figure 5C) (Kuttner et al. 2018). This is the first report that AuNTs may overgrow and retain their well-defined truncated triangular bipyramidal morphology as they increase in size. In addition to the commonly used seed-mediated growth synthesis for preparing SERS substrates, special types of periodic plasmonic nanostructures can be constructed, such as nanostructured metal, which can be achieved by depositing thin films of metals on ordered arrays of dielectric microspheres. Starting with the development of most SERS substrates in air, since the optical properties of metal nanostructures are mainly influenced by the refractive index of medium, some authors have studied the optical properties of metal coated microspheres arrays in aqueous environments, found that the variation of medium can cause the change of absorption band, and the utilization of this phenomenon can achieve the desired performance of SERS (Nechita and Farcău 2021).

In addition to a single nanoparticle layer, some works are more inclined to use two or even multi-layer metals to produce more suitable gaps between nanoparticles for the study of "hot spots." Tian et al. reported a special method to obtain high-density, monodisperse Au@Ag core-shell NPs (Tian, Zhang, et al. 2019). AuNPs are deposited on a one-dimensional support by laser, followed by cetyltrimethylammonium chloride (CTAC)-assisted Ag shell overgrowth on the Au core (Tian, Zhang, et al. 2019). In situ deposition of silver on the surface of acicular AuNPs can form spines Au@Ag Core-shell NPs (Huang et al. 2019). The silver coatings were wrapped on top of the AuNPs with outstanding stability and controllable particle size, and 4-MBA was embedded between them so that the Raman reporter would not be easily fall off to ensure the stability of sensing (Liao, Liu, et al. 2021). What's more, in the light of electromagnetic theory, Au provides greater chemical stability while Ag is more effective than Au in plasmonic enhancement. Therefore, Das et al. synthesized Au-Ag bimetallic nanostructures (Figure 5D) by combining the advantages of the two materials and captured SERS signals at lower concentrations (Das et al. 2021). Compared with spherical shell structure, this structure can produce stronger electromagnetic field and exhibit better SERS activity. Modification of Au-Ag bimetallic nanoparticles on silicon nanowires improve the activity of the 3D SERS substrates via the synergistic effect of gold and silver particles, and the SERS substrate show high EF (10^8) and antioxidant capacity as well as ultra-low detection limit (10^{-12} M) (Liao, Liu, et al. 2021). When examining crystal violet (CV), the Raman intensity of the bimetallic Au/Ag self-assembled monolayer is 223 times stronger than that of the gold nanoparticles alone (Tian et al. 2018).

Metal-organic frameworks

To date, hollow nanostructures with various morphologies have been developed, such as spherical nanoshells and nanoframes (NFs). To take full advantage of the structural advantages of NFs for plasmonic applications, Lee and his colleagues designed an unprecedented nanoframe structure, that is, particle-in-a-frame nanostructures (Lee, Lee, et al. 2019). Through Finite-Difference Time-Domain (FDTD) simulations, the novel structure shows large LSPR sensing sensitivity and high SERS activity, thanks to the strong electromagnetic field at the inner small nanogap (average gap size is 1.0 nm) (Lee, Lee, et al. 2019). Metal-Organic Frameworks (MOFs), an emerging crystalline porous material, are organic-inorganic hybrid materials with intramolecular pores formed by the self-assembly of organic ligands and metal ions or clusters through coordination bonds. As a protective layer, MOFs can overcome the poor stability of noble metal substrates in complex environments, and have achieved tremendous achievements in a variety of applications such as gas adsorption, storage and separation, catalysts, and bioimaging (Jiao et al. 2019). Huang et al. reviewed recent advances in the field of MOF-SERS systems and introduced their unprecedented capabilities (Huang, Li, et al. 2020). Although the design strategy of the MOF-SERS system is briefly introduced, the applications of the unique properties of the MOF structure are summarized in detail, which are thoughtful for the further development of the research on MOF-SERS substrates (Huang, Li, et al. 2020). The preparation methods and optical properties of nanoporous metal networks are reviewed by Ron et al. Nanoporous networks are also porous materials, consisting of solid metals, possessing unique optical properties, high specific surface area and outstanding permeability (Ron, Haleva, and Salomon 2018). However, the wavelength of its particles and voids and the preparation of large-scale metal networks are not particularly ideal.

The development of SERS technology extends to single-molecule detection with excellent molecular fingerprinting capabilities. As a promising ultrasensitive analytical technique, it has potential applications in the detection of volatile organic compounds (VOCs) (Chen, Liu, et al. 2021; Zhang, Chen, et al. 2021). However, this application is currently limited by the weak Raman signal of the markers and the low adsorption of gaseous molecules by solid matrices with the high mobility of gaseous molecules. Qiao et al. coated the surface of self-assembled Au superparticles (AuSP) with a ZIF-8 layer to slow the flow rate of gaseous markers and suppress the exponential decay of the EM field around the AuSP surface (Qiao et al. 2018). Tumor-specific tissue composition and metabolically released gaseous aldehydes can be used as indicators of lung cancer, which are guided through ZIF-8 channels and captured onto SERS-active AuSPs substrates with a detection limit of 10 ppb, showing excellent promise in vitro diagnostics of early-stage lung cancer (Qiao et al. 2018). Fu et al. demonstrated that MIL-100(Fe) composed of Fe clusters and 1,3,5-benzenetricarboxylic acid serves as an ideal SERS-active substrate to recognize and capture a variety of VOCs (Fu et al. 2020). Particularly, the modified MIL-100 (Fe-Zr) material can selectively sense whether the substituted metal atoms in VOCs and MOFs have more high affinity. This variability and extensibility facilitate the construction of "array sensors" with higher sensing performance for different odors. In addition, the reusability of the MIL-100(Fe) substrate is also tested by repeating the adsorption-desorption process, and the experiments show that MIL-100 (Fe) exhibit favorable regeneration performance for at least 10 cycles, greatly promoting potential applications of this substrate (Fu et al. 2020). The SERS platform prepared by MOF can be used to aggregate gas molecules due to the particularity of the structure. Kim et al. used the SERS paper prepared by MOF to detect putrescine and cadaverine to explore whether food has spoiled (Kim, Kim, et al. 2021).

Polymer film

Polystyrene

Polystyrene (PS) is a familiar polymer material, which is widely used in the preparation of SERS substrates in the form of microspheres. Frequent PS microsphere preparation methods include emulsion polymerization, suspension polymerization, dispersion polymerization, seed swelling, and soap-free polymerization. After the first report of PS microspheres, the preparation and research of polymer microspheres have become one of the hottest directions in the field of polymer research. Furthermore, PS microspheres are widely used in electrochemical detection and preparation of SERS active substrates due to their excellent properties such as strong adsorption, small particle size, large specific surface area, and easy modification and decoration.

Zhang et al. prepared PS microspheres and deposited them on silicon spheres, and modified silver nanoparticles on the top layer (Zhang, Li, et al. 2017), and found that the intensity of the Raman spectrum is the largest when etching for 5 minutes. When detecting R6G, the EF is as high as 2×10^{14}, and the detection limit is as low as 10^{-15} M. Silver nanoparticles were assembled on PS spheres and used as biosensors to detect pesticide residues (Zhang, Chen, et al. 2021). Based on the tape imprinting method, a novel double-sided activated high-performance SERS substrate was developed (Wang, Sun, et al. 2019). The substrate come with 3D fully spatially distributed hot spots derived from layered lotus root-like Ag arrays, providing ultrasensitive, reproducible, uniform, and reliable quantitative measurements. This well-performing SERS substrate also hold great promise for practical in situ molecular detection on curved surfaces, which is not yet possible for SERS of conventional rigid materials.

Combining two common substrate preparation methods, top-down etching and bottom-up self-assembly, the former created rainbow patterns recognizable to the naked eye, and the latter produced subwavelength nanoscale features (Liu et al. 2016). The butterfly pattern of PS microsphere array can be etched with a cost-effective commercial laser engraver, followed by the normal process of depositing silver nanoparticles on a flexible polymer film. From the partial SEM images of butterfly wings, it can be observed that the silver-coated PS microsphere arrays have a high degree of homogeneity, and the formation of rainbow light is related to the interference, diffraction and scattering of these periodic arrays. The rough surface observed in Figure 6A(c–f) provides the basis for the strong SERS signal. The research group can help preserve privacy by simply encoding and hiding the information with knowledge of the dye (Liu et al. 2016). Although the example reported by the research group is relatively simple, it provides a new direction and possibility for the application of flexible substrates. The only regret is that although the current lithography technology is relatively mature, the reports on the preparation of large-area substrates and the plasmonic metasurface area are still limited.

Silver was coated on PS nanopillars, and there would occur strong plasmonic coupling between adjacent gold nanopillars and small nanogap, with an optimal gold layer thickness of 30 nm, a detection limit of 10^{-9} M was obtained when detecting 4-MBT molecules, and the relative standard deviation of SERS signal was 8% (Kim et al. 2017). As illustrated in Figure 6B, firstly using PS monolayer colloidal crystals on Si wafer as a template, the deposited gold was annealed to obtain Au NS arrays. Then, the silver film was modified on the Au NS arrays, and the solidified Au-Ag alloy array was obtained after annealing. After the array was finally dealloyed with nitric acid, the porous Au-Ag alloy array was fabricated (Zhang, Huang, et al. 2018). Based on the hybrid structure of PS spheres, the two nanoparticle layers of gold and silver are separated by a cap-like MoS_2 film. Because of the spatial curvature and narrow gap of the MoS_2 film, the active substrate for SERS exhibits superior detection performance (Zhang, Chen, et al. 2021).

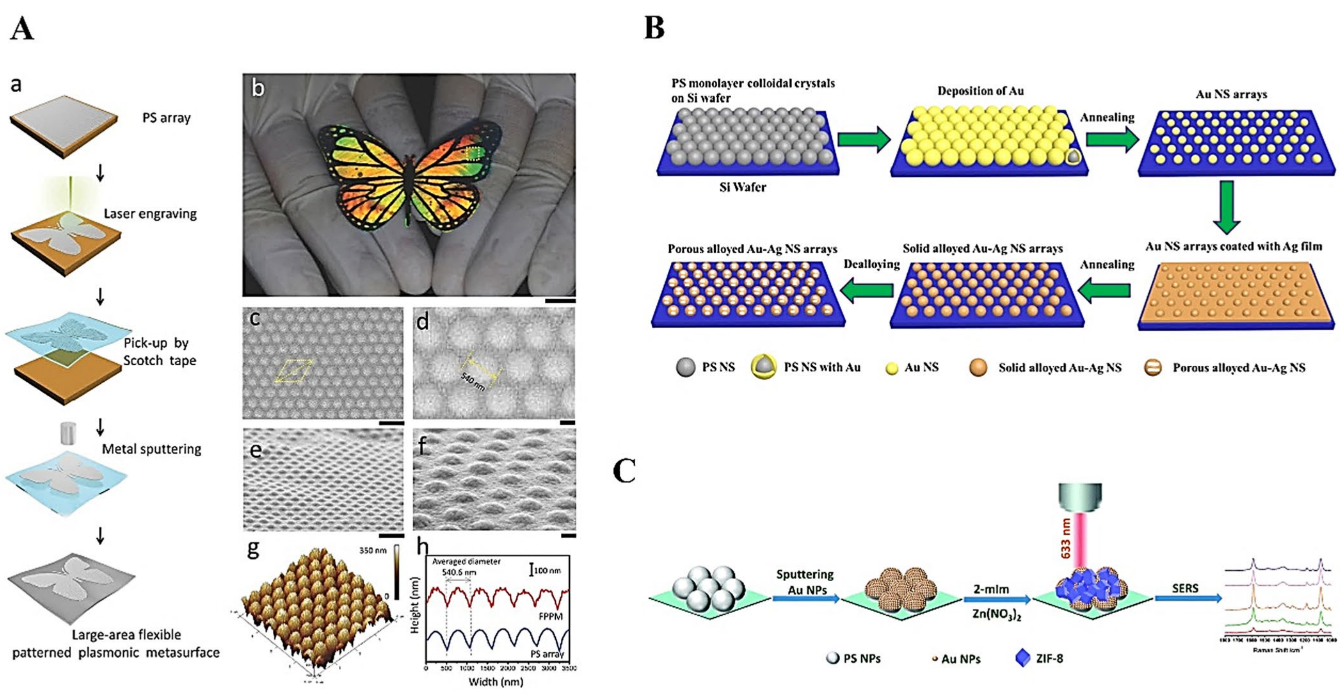

Figure 6. A) Construction of large-area flexible plasmonic metal films and their characterization. Reproduced with permission (Liu et al. 2016). Copyright 2016, John Wiley and Sons. B) The Synthesis of Porous Alloyed Au-Ag nanosphere Array. Reproduced with permission (Zhang, Huang, et al. 2018). Copyright 2018, American Chemical Society. C) Schematic diagram of the construction and detection of the PS/Au/ZIF-8 substrate. Reproduced with permission (Xue et al. 2021). Copyright 2018, Royal Society of Chemistry.

Xue et al. successfully put PS/Au templates into a mixture of 2-methylimidazole (2-mIm) and Zn $(NO_3)_2$ for reaction, thereby adding ZIF-8 to the surface (Figure 6C). Since ZIF-8 provides a large surface area and thus has a strong adsorption capacity for probe molecules, the SERS signal is naturally enhanced (Xue et al. 2021). PATP at 10^{-17}M concentration was observed in "hedgehog-like" arrays prepared on PS nanospheres by Guan et al. Moreover, according to what they given, methylene blue (MB) molecules are plasmon-catalyzed degraded by strong surface plasmon resonance enhancement (Guan et al. 2019). By combining the catalytic process and SERS, the in-situ SERS study of the plasmonic photocatalytic degradation of MB molecules is completed. This is a report for the first time of in situ monitoring of plasmonic nanochemical reactions using plasmonic thin films without any traditional catalytic materials.

Similarly, Zhang et al. simplified the method to deposit gold on PS spheres to obtain a large-scale granular Au nanocap ordered array (Zhang, Peng, et al. 2020), but the detection limit of the flexible substrate obtained by this method is significantly reduced. 3,4-dihydroxyphenyl-L-alanine (L-DOPA) is polymerized by oxidative polymerization under alkaline conditions, and its polymer (i.e., PLDOPA) provides high adhesive properties. The oxidative polymerization of L-DOPA was deposited on PS NSs through many interactions to form conformal PLDOPA films, stabilizing the surface gold nanoparticles (Calis and Yilmaz 2021). Finally, the PS@PLDOPA@Au-NP systems exhibited excellent properties in both catalytic activity and SERS tests. An innovative droplet deposition method decorates silver nanoparticles on the PS substrate instead of depositing the nanoparticles on the entire PS substrate (Tsao et al. 2021). Owing to the hydrophobicity of PS, sample droplets can be concentrated and manipulated at interesting locations, which can effectively to improve detection sensitivity.

Polydimethylsiloxane

Polydimethylsiloxane (PDMS), a hydrophobic organosilicon material, has attracted extensive attention in the preparation of flexible SERS substrates due to its high transparency, good heat resistance, stable chemical properties, and water resistance. For instance, as illustrated in Figure 7A, Kumar et al. embedded Ag nanorod arrays into PDMS films (Kumar, Khosla, et al. 2017), and the performance of the prepared substrates was no worse than that of Ag nanorod arrays deposited directly on silicon/glass sheets, while flexibility, mechanical stability, and portability were greatly improved.

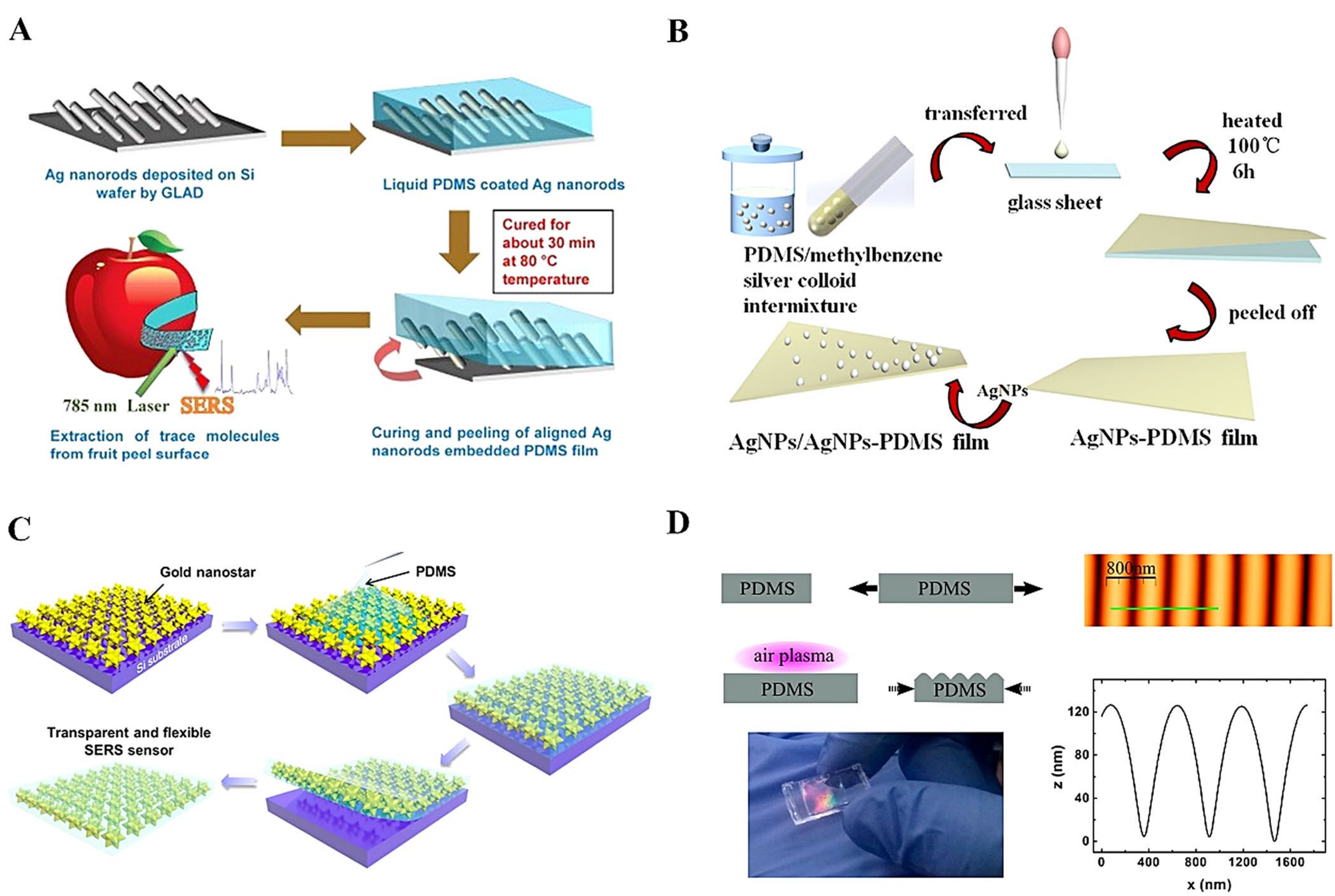

Figure 7. Schematic illustration of the fabrication of A) AgNRs embedded PDMS flexible substrate. Reproduced with permission (Kumar, Khosla, et al. 2017). Copyright 2016, Elsevier B.V. B) the AgNPs/AgNPs-PDMS substrate. Reproduced under terms of the CC-BY license (Guo et al. 2018). Copyright 2018, the Author's. Published by OSA. C) Flexible SERS sensor constructed from gold nanostars and PDMS. Reproduced with permission (Park, Lee, and Ko 2017). Copyright 2017, American Chemical Society. D) Construction of periodic nanostructured PDMS templates. Reproduced with permission (Barelli, Repetto, and de Mongeot 2019). Copyright 2019, American Chemical Society.

Park reported that transparent substrates obtained with PDMS film embedded with gold NSs exhibited ultrahigh flexibility and sensitivity (Park, Lee, and Ko 2017), and Raman reporters on the surface of the SERS active layer exhibited very strong signals because of the special structure of gold NSs (Figure 7C). The Ag-NPs/PDMS composite membrane has good adhesion thanks to the "sticky" property of PDMS, which can be used for in situ detection (Alyami, Quinn, and Iacopino 2019).

Figure 7D shows the fabrication process sketch of the PDMS nanosubstrate and the atomic force microscope (AFM) image of the corrugated PDMS substrate and its outline (Barelli, Repetto, and de Mongeot 2019). The method to form a substrate by depositing arrays of Au nanowires on the surface of the wrinkled PDMS film is simple and facilitates large-area production, and the substrate exhibits multifunctional properties such as transparency, tunable plasmonics response, flexibility, and so on. Gou et al. aminated the PDMS layer and then modified it with AuNPs (Gou et al. 2021). On this basis, they constructed a two-layer leaf-vein-like microfluidic device in which cells moved and finally achieved specific binding to antibodies. The capture of up to 91.2% of breast cancer cells makes the device have great potential in the application of multi-circulating tumor cell capture. The Au shell-coated AgNPs were deposited on the PDMS film, and the Au shell layer improved the oxidation resistance of the AgNPs, which improved the stability of the flexible substrate and maintained the SERS activity for a long period of time. Owing to the ultra-thin Au shell, the dielectric properties of Au-coated AgNPs are still dominated by AgNPs, thus, the Au-coated AgNP/PDMS substrate can be used for pH sensing with 4-MBA under laser irradiation at 532 nm (Fortuni et al. 2017). Cheng and colleagues modified the surface of PDMS substrates by N_2-plasma treatment to form a hydrophilic vitrified surface layer. By means of plasma treatment, the contact angle of the PDMS substrate was reduced from 115.4° to 32°, resulting in a hydrophilic surface (Cheng et al. 2020). Furthermore, uniform Au-Ag NP arrays were deposited on plasma-treated PDMS substrates for SERS detection. Since the gap between the NP arrays could be narrowed by the plasma treatment, the substrate sensitivity and Raman signal were enhanced, which indicated that the gap between Au-Ag NPs could be effectively regulated by bending the PDMS-based substrate.

Recently, a 3D microlens array/wrinkled structure/AgNPs SERS substrate (MLA/WS/AgNPs 3D-SERS) was reported (Zhang, Chen, et al. 2022). The ordered micro-nano hierarchical structure array expanded the multi-dimensional distribution of hot spots for higher sensitivity, and could also ensure uniform distribution of hot spots to acquire good uniformity. Additionally, the comprehensive properties of the SERS substrate were also systematically investigated and found that the substrate has excellent properties and could be stored under natural conditions for about 20 days with little loss of performance. Wang et al. reported a flexible microsphere-coupled SERS substrate consisting of a dielectric microsphere cavity array (MCA) and random AuNPs, which was overlaid on a PDMS film (MCA/AuNPs/PDMS) for enormous enhancement (Wang, Xu, et al. 2022). The homogeneity of the SERS substrate was further confirmed by the Raman intensity histogram, whose RSD decreased by an order of magnitude from 47.4% to 5.3% of the bare PDMS substrate (Wang, Xu, et al. 2022). The uniform spatial distribution of intensity guarantees the reproducibility of Raman detection of MCA as a microsphere-coupled SERS (McSERS) substrate. It can be explicitly confirmed that the PDMS support substrate is beneficial for the flexible application of McSERS substrates. Ultimately, the substrate exhibits brilliant compatibility and durability as an ultrasensitive Raman test strip. A nano-micro hierarchy was reported on a flexible PDMS layer as a SERS stamp for ultrasensitive detection (Gao et al. 2020). Thanks to the multi-scale coupled EM enhancement mechanism, the structure generated a huge SERS signal with AgNPs. Highly ordered nanowrinkles were fabricated using oxygen plasma and PDMS stretching treatments. As a matter of fact, the intelligently designed zigzag micropatterns effectively reduced the fracture defects of nano-wrinkles because the shrinkage force was lessened during the release phase. Therefore, the substrate exhibits high uniformity and reproducibility in the experiments, with an RSD of less than 7% (Gao et al. 2020).

Moreover, metal particles can also be deposited on the PDMS layer embedded with metal nanoparticles, so that in addition to the particles in the flexible film and the particles on the surface layer, the metal nanoparticles between the two layers can also interact to obtain the final results. The sensitivity of substrate can also be further improved. The AgNPs/AgNPs-PDMS substrate structure presented by Guo and his colleagues is based on this principle (Figure 7B) (Guo et al. 2018). Large particle spacing will result in a lack of inter-particle coupling, which affects the hotspot density. Therefore, in order to achieve stronger coupling of bilayer metals, some scholars have designed the underlying film into nanocone arrays. First, the Alumina was designed into a cone shape, then a layer of silver nanoparticles was sprayed on it, and then poured and cured with PDMS to obtain its complementary structure, that is, PDMS filled the silver nanocavity array (Guo et al. 2018). Similar designs have been suggested by modifying a layer of gold nanoparticles on it (Zuo et al. 2022). The optimal multiple plasmon coupling is obtained by adjusting the height of the nanocones and the deposition thickness of the surface gold. Apart from applications of PDMS on flexible SERS substrates, it can also be used to prepare flexible metamaterial for tuning the resonances of terahertz metamaterial (Xu and Lin 2019).

Polymethylmethacrylate

High repeatability and low cost are the two most valuable requirements for SERS technology in practical applications. Polymethylmethacrylate (PMMA), also known as plexiglass, is often used as a glass substitute material with light density, high transparency, cost-effective and high mechanical strength. An affordable, simple, and efficient method for fabricating SERS substrates is proposed. A large area SERS substrate was prepared by depositing a silver layer onto the dewetting droplet structure of the PS/PMMA blend film, and when the blending ratio was 1:1, the average spacing between droplets was narrowest and the droplet diameter distribution was smallest (Zhang, Xu, et al. 2016). Moreover, the substrate of 8 nm shows outstanding reproducibility and higher EF. Nevertheless, a volcano-shaped PMMA film can be constructed by PS spheres, and then the volcano-shaped PMMA substrate is immersed in a stable AuNP solution, and the AuNPs are adsorbed in the volcano-shaped PMMA film due to van der Waals forces and electrostatic interactions (Chang et al. 2022). Naturally, when the pore size of the volcanic PMMA is larger to a certain extent, the larger the metal particles adsorbed by the hybrid substrate film, the more "hot spots" it presents.

Due to the rapid evaporation of the volatile solvent in PMMA, single-gold nanocube-structured AuNCs were spontaneously formed within the PMMA pores when the gold precursor PMMA dispersion was spin-coated on N-doped silicon wafers (Omar et al. 2017). Adjusting the precursor concentration can control the size of the nanocubes. Some scholars change the size of the AuNCs by changing the Au^{3+} concentration. Using pyridine as the probe molecule, the detection limit of 10^{-12} M can be achieved, and it is evaluated as an ultrasensitive SERS sensor (Omar et al. 2017). The preparation of gold nanostars by photoreduction of gold precursors and ethanol was first reported by Riswana Barveen, Wang, and Chang (2022). This one-step method has simple reactants, short reaction time, simple preparation process, and is environmentally friendly, which is suitable for mass development. Gold nanostars were attached to flexible PMMA to obtain AuNSs/PMMA SERS substrates, which can be used to detect ciprofloxacin (CPX) and chloramphenicol (CAP) (Riswana Barveen, Wang, and Chang 2022). It shows many attractive characteristics, such as high sensitivity, high EF, excellent mechanical stability, multiple detection and so on. PMMA was spin-coated on a 50 nm gold film, and the prepared 170 nm AuNCs solution was dropped on top to form a AuNCs-PMMA-gold thin film (Wang, Sun, et al. 2019). The study found that compared with the single AuNC structure, the composite structure can excite the propagating surface plasmons at the interface of PMMA and Au film as well as the local surface plasmons of Au nanocubes. Moreover, strong coupling resonance also occurs between LSP and PSP, leading to the generation of very high electric field enhancement effect and strong SERS signal (Wang, Sun, et al. 2019).

Supported AgNFs growth by graphene-templated microcurrent-assisted chemical reduction, Ag nanoflowers with uniformly distributed nanotips can generate huge EFs and dense hot spots. Furthermore, graphene can effectively stabilize the SERS signal and protect AgNFs from oxidation. Therefore, the graphene/Ag-nanoflowers/PMMA flexible substrate prepared by Qiu et al. has high sensitivity and long-term stability (Qiu et al. 2017).The composite structure of Au nanocubes was deposited by Au film/PMMA gratings as the SERS substrate (Wang, Sun, et al. 2021). The detailed preparation diagram is shown in Figure 8A(a). The original design is to create strong coupling between the gold nanocubes and the grating, so that the local electric field must also increase by several orders of magnitude. The properties of the substrates were investigated by PDTD and Raman spectrometers, and it was found that the experiments and the theory are in good agreement, indicating that the properties of the prepared substrates are very good. A novel SERS substrate was designed by depositing SERS-active metal nanoislands on atomically planar graphene layers, termed graphene-mediated SERS (G-SERS) substrates (Xu et al. 2012). The signal from the G-SERS substrate was also shown to have interesting advantages over ordinary SERS, with clearer vibrational information unaffected by various metal-molecular interactions, more robust to photo-induced damage, and comparable EF. Together with the PMMA layer as the support for the monolayer graphene and the sandwiched metal nano-island group, a transparent, free-standing and flexible "G-SERS tape" was demonstrated (Xu et al. 2012). Direct, reliable, and real-time detection of trace analytes in various systems is achieved, which endows G-SERS substrate analysis with universality and high efficiency.

The polymer PMMA protective film was spin-coated on the dimer array, and the obtained flexible SERS chips were used to identify the dyes in the ink (Hao et al. 2020), the details of the preparation process are illustrated in Figure 8B. The letters written on the plastic material are erased. Since Rhodamine B(RhB) was adsorbed on the plastic material, the erased letters can be clearly seen in the two-dimensional Raman spectrum, as shown in Figure 8B(e), which provide potential applications for identifying ancient calligraphy and texts. In-situ real-time SERS measurements can also be performed in liquid environments, and the reduction of PNTPs to PATP in the absence of chemical reductants was observed by in situ liquid Raman measurements (Hao et al. 2020). Fahes et al. also precisely controlled the shape, size, and interparticle spacing of silver nanoparticles in PMMA through a simple and time-consuming vapor-phase induced phase separation (VIPS) method to generate a large-area active SERS substrate (Fahes et al. 2021). With the help of silicon plate support to form 3D pyramid structure and PMMA to form flexible substrate, the larger specific surface area can attach more metal nanoparticles and generate more hot spots. Xiu's team constructed GO/AgNPs/Pyramid PMMA 3D flexible substrates in a low-cost way (Xiu et al. 2018). Additionally, the substrates with good adhesion and flexibility as well as pyramidal structures enable the assembly of target molecules, thus, such flexible substrates have the ability to directly contact with surface analytes for high-sensitivity detection.

The precursor solution of silver and flexible PMMA are incompatible, so that the final formation of nanopores, and the PMMA layer acts as a coating carrier for silver nanoparticles, which can protect them from external physical and chemical changes. The formation principle of AgNPs/PMMA flexible film has been specifically analyzed (Wang, Sun, et al. 2021). Acetone solution is capable of dissolving PMMA. Therefore, when PMMA molecules in acetone are in contact with silver nanoparticles, the carbonyl functional group of PMMA can act as a binder to adsorb silver nanoparticles. Since acetone is volatile when heated and the PMMA solution is cured, the AgNPs firmly adhere to the polymer film

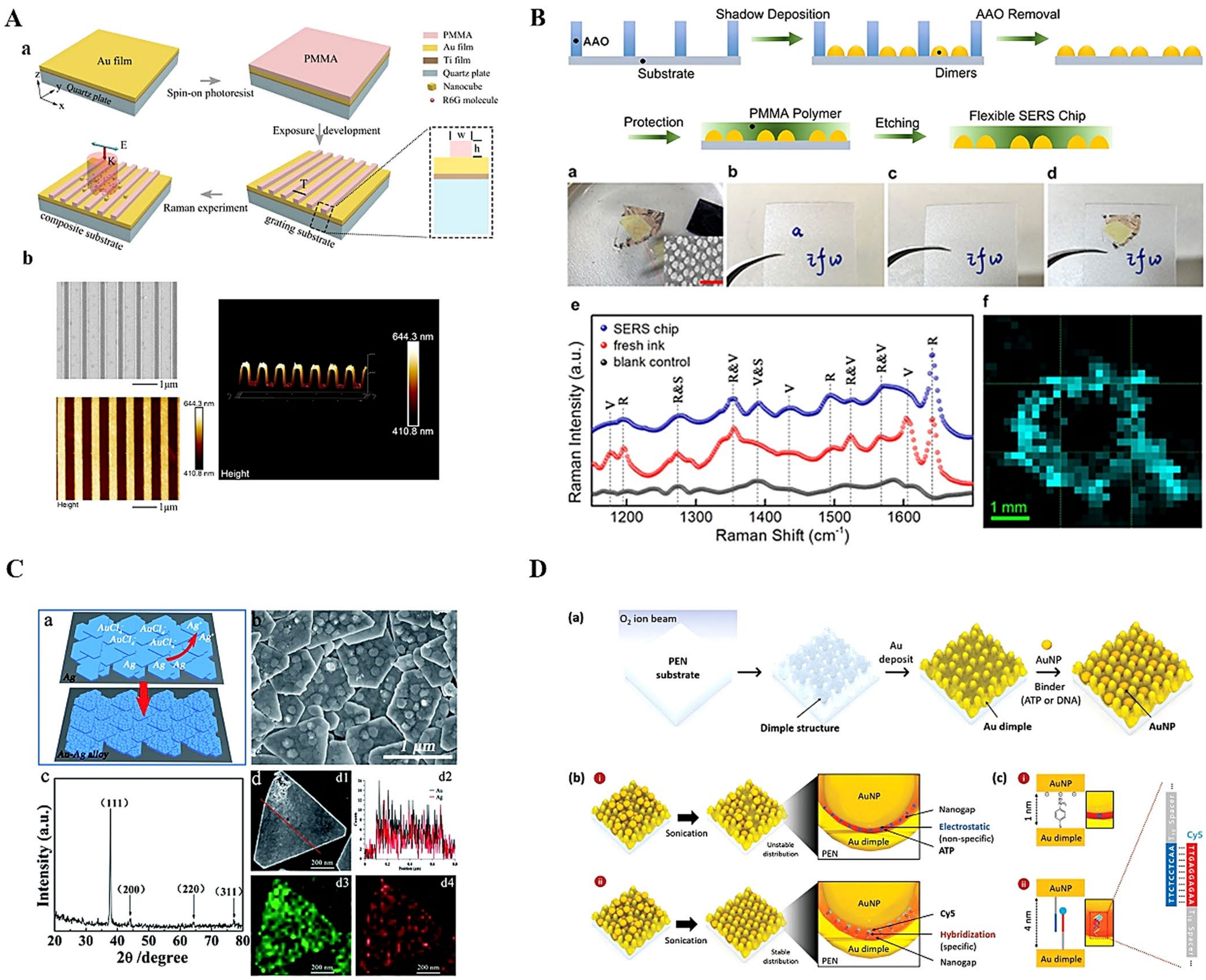

Figure 8. A. a) Schematic diagram of the fabrication process of the gold film/PMMA grating coated with gold nanocubes and the cross-sectional view of a single grating period, b) SEM and AFM of the grating substrate, and cross-sectional view of the AFM height image in the grating substrate. Reproduced with permission (Wang, Sun, et al. 2021). Copyright 2021, Elsevier B.V. B. Schematic diagram of the fabrication process of the flexible SERS chip and in situ identification and characterization of the colorant of the flexible chip. Reproduced with permission (Hao et al. 2020). Copyright 2020, American Chemical Society. C. a) Schematic diagram of the electro-displacement reaction at the solid-liquid interface between the Ag nanoplate film and HAuCl4 solution, b) SEM image of the gold-silver alloy nanosheets on the transparent PET film, c) dark-field of the Au-Ag alloy nanosheet film Scanning Transmission Electron Microscopy (STEM) and Elemental Mapping. Reproduced under terms of the CC-BY license (Sun, Liu, et al. 2017). Copyright 2017, the Author's. Published by RSC Advances. D. a) Schematic diagram of fabrication of Au nanodimpled substrate and internalization of AuNPs, b) internalization of AuNPs in the cavity of nanodimpled substrate by i) electrostatic interaction and ii) DNA hybridization and c) internalization interaction force. Reproduced with permission (Dang et al. 2021). Copyright 2021, John Wiley and Sons.

upon peeling. The higher the concentration of PMMA solution, the stronger the absorption intensity because of the increased in the amount of metal particles it adsorbs (Wang, Sun, et al. 2021). In the detection of pesticide residues on the curved surfaces of fruits and vegetables, it was found that the flexible substrate has a high EF and an ultra-low detection limit, which is expected to be applied in real-time detection in the field.

Polyethylene terephthalate

Polyethylene terephthalate is referred to as PET, commonly known as polyester resin. It has low cost, highly flexible, low weight, good optical transparency, and highly porous material. and is also widely used in the preparation of SERS active substrates. Moreover, PET polymers can also assist in the formation of bilayer microgel/substrate films at higher temperatures (Tian, Li, et al. 2017). PET modified with oxygen plasmonics can increase the viscosity with gold nanoparticles, as well as change the growth kinetics of gold nanoparticles, affecting the degree of freedom (Bianco et al. 2013). The silver nanoparticle ink was printed on the PET surface, and the best SERS signals can be obtained by controlling the surface roughness (Emamian et al. 2015). Similarly, the modified PET was coated with a layer of silver nanoparticles, and the good flexibility allowed the substrate to be used for in-situ detection on objects of any shape (Zuo et al. 2016).

Sun et al. deposited silver nanoplates on a PET film, and then obtained an Au-Ag alloy nanoplate film with controllable surface roughness and enhanced electrical conductivity through a galvanic displacement reaction with the gold precursor solutions (Sun, Liu, et al. 2017), shown in the Figure 8C. Densely-arranged Au@Ag NP arrays are conveniently embedded into flexible, smooth, and sticky acrylic polymer tape using a simple press, and then cover with PET film to block disturbance from the surrounding environment. The polymer multi-layer encapsulated SERS chip have the characteristics of high mechanical stability, uniform signal distribution, and good long-term storage stability. In SERS measurement, the PET film can be easily peeled from the substrate. Its flexible nature allows the adhesive SERS tape to adhere tightly to curved surfaces, providing the ability to sample analytes for SERS detection. Therefore, the structure of Au@Ag nanoparticle array sandwiched between adhesive acrylic polymer tape and PET film (T/Au@Ag/PET) can be used as a high-performance SERS chip (Wang, Sun, et al. 2021). Silver wire was used as a vaporizing raw material to stack on highly transparent PET (Li, Wang, et al. 2018), and when four layers were deposited, the accumulation of metal layers maximizes the "hot spots" density enhancement and the Raman signal.

To engineer the ordinary nanoparticles into shapes such as gold nanoflowers in PET synthesis, the tips of the nanoflowers could also create more "hot spots" (Lu et al. 2019). Furthermore, in order to save cost and reduce the thickness of the silver layer, a flexible active PET/ITO/Ag SERS platform was developed by covering a layer of indium tin oxide (ITO) with PET (Nowicka et al. 2019). Wang et al. showed that PET film as a barrier for Au@Ag/PMMA/qPCR film could improve the stability of SERS chips (Wang, Sun, et al. 2019). The whole chip fabrication process is flexible and easy to operate, which provides a new strategy for wearable sensors. Many silver nanoparticles were attached to the ZnO nanosheets of semiconductor material on PET plates, which was a cavity-based particle-in-quasicavity (PIQC) architecture designed by Yu et al. (2020). The structure can provide a dense and large hot spot, and the SERS chip exhibits excellent stability, repeatability and uniformity during detection, which is of great benefit to the application of constant monitoring. The surface of PET film was modified with polydopamine to grow 3D ZnO nanorods/Ag nanocomposites in situ. Moreover, Cheng's team used this multilayer structure to study the mechanism of photocatalytic activity and SERS enhancement, and showed that appropriately affecting the recombination of photo-induced electron-hole pairs can improve the photocatalytic efficiency effectively (Cheng et al. 2021). In a study done by Ndilowe et al., it was reported that more AgNPs could be attached to the PET surface after modification with diethylenetriamine (DETA) (Ndilowe et al. 2021).

Polyethylene naphthalate (PEN) is one of the important members of the polyester family and an emerging excellent polymer. Its chemical structure is similar to PET, but PEN has higher physical and mechanical properties, chemical stability, heat resistance and UV resistance than PET. PEN substrates with nano-dimples were prepared by oxygen ion beam sputtering (Dang et al. 2021). After depositing gold films, AuNPs were inserted into the curved cavities of nano-dimples gold substrates using two methods of electrostatic interaction of 4-ATP and DNA hybridization (Figure 8D). Moreover, SERS-PCR using this system can be used to detect COVID-19 DNA biomarkers, about 100 times lower than the detection limit obtained by conventional RT-PCR (Dang et al. 2021). In addition to the aforementioned substances that modify the PET film, argon plasmonics could modify the PET film into nano-columns, and the minimum detection limit of R6G on the worm-shaped SERS substrate formed after the deposition of gold nanoparticles could also reach 10^{-9} M (Zang et al. 2021). Recently, microfluidic technology has enabled the analysis of Raman signals with excellent reproducibility and high precision, and its applications in SERS technology are also increasing. However, injection molding of cyclic olefin copolymers (COP) has also become a preparation method for microfluidic devices. Gutiérrez et al. used COP combined with silver-coated PET polymers to prepare SERS chips (Gutiérrez et al. 2022), which avoided the interference of long working distances and strong fluorescent signals, to this end, the resulting signal can remain stable for several months.

Cellulose fibers

Paper

Commonly used flexible materials are paper, fabric, cellulose fibers, polymers, and so on. However, the hydroxyl groups on the fiber surface of paper will combine with AgNPs, and filter paper can be used as a suitable carrier material for noble metal nanoparticles. Paper is a promising SERS substrate candidate due to its porosity, high hydroxyl content, strong capillary driving force, and large specific surface area. Metal nanomaterials can be loaded on filter paper, but the density distribution of nanomaterials is not necessarily high because of the hydrophilicity of the paper. Wang et al. modified silver nano-triangles on filter paper and achieved certain results (Wang, Liu, and Dou 2016). Some scholars treated the filter paper with alkyl ketene dimer (AKD) to change it from hydrophilic to hydrophobic, and the enrichment of AgNPs increased and the number of hot spots also increased (Lee, Hung, et al. 2018). By preventing the rapid absorption of the analyte by the filter paper, the retention time of the analyte is increased. As the number of SERS hots pots increasing, the SERS signal is strongly enhanced because of the increasing density of AgNPs on the small contact area of the filter paper surface. By controlling the distribution of AgNPs on the surface of the filter paper, the reproducibility and sensitivity of the SERS signal are optimized. Pagano et al. designed an affordable and simple method for silver nanodisc SERS substrates with filter paper for the detection of tetracyclines in water (Pagano et al. 2021). SERS analysis with filter paper as the substrate also enabled the quantification of acetylsalicylic acid in commercial tablets (Sallum et al. 2014). This method has low synthesis cost and fast SERS spectroscopy with low sample preparation and reactant amounts.

In addition, paper was also used in paper centrifugation chromatography methods for rapid separation and qualitative analysis of multicomponent substances (Gu, Li, et al. 2021). He et al. developed a low-cost, lightweight, high-sensitivity AuNS-immobilized paper-based SERS substrate that could be fabricated in any laboratory (He et al. 2017). The enhancement coefficient of the optimized AuNS-filter paper substrate is higher than that of the two commercial Au/Ag-based SERS chips. This optimized dry-substrate and wet-analyte configuration meant that paper-based SERS substrates can be stored prior to use and immediate Raman acquisition is possible without sample drying (He et al. 2017). Lee et al. developed a facile solid-liquid interface reduction reaction to manipulate the secondary growth process of Au nanostructures on soft filter paper (Lee et al. 2021). The obtained Au nano-branched SERS substrates provided several SERS enhancement sites and exhibited analytical enhancement factors of $1.4–7.4 \times 10^5$. Compared with the original SERS sensing, the enhancement is increased by more than 6 times, resulting in a reduction of the detection limit to several ppb (Lee et al. 2021). Alternatively, the zoomed negative pressure to implement vacuum filtration caused the AgNPs to intercalate into the micropores of the filter paper membrane, increasing the mechanical binding to the filter paper membrane (Zeng et al. 2019). Undoubtedly, in addition to the morphological change of the paper surface plasmon, the paper thickness, uniformity, and endogenous fluorescence will all have an impact on the preparation of the SERS substrate (Oliveira et al. 2017). Therefore, the selection of high-quality paper is crucial for the detection effect.

The filter paper was first cleaned and smoothed, and then AgNS was grown in situ on Whatman filter paper (grade 42) by a simple one-step silver mirror reaction to fabricate the SERS sensor (Verma et al. 2021). However, to prevent the oxidation of AgNS on the paper base, all paper SERS substrates are kept in a vacuum desiccator, so the base is highly stable and reproducible during characterization. Shinki and Subhendu Sarkar compared several inexpensive daily-routine materials such as A4 printing paper, sandpaper, transparent tape, carbon, aluminum foil, and shredded aluminum foil (Sarkar 2022). Using these as flexible substrate supports respectively then depositing plasmonic active Au-Ag alloy nanolayers of the same thickness on the surface will make all the substrates SERS active. It was found that the fractured aluminum foil combines the advantages of Au-Ag alloy nanolayers and exhibits a higher SERS response without the need for time-consuming pretreatment and additional chemical methods (Sarkar 2022). Tian et al. introduced a pen-on-paper (POP) method to fabricate POP wire SERS substrates with selectable plasmonic NPs (Tang et al. 2016). Hydrophilic SERS active lines are obtained by direct writing on hydrophobic poly (L-lactic acid) nanofiber paper using a pen filled with plasmonic NP ink. The POP-line SERS substrate have a hydrophobic-hydrophilic focusing effect, high sensitivity, negligible Raman background interference, and good reproducibility and long-term stability. Recently, the popular inkjet-printed plasmonic paper-based SERS platform with high SERS efficiency reported by Godoy et al. (2020). The high stability of the ink in this substrate (over 1 year of storage) and the surface modification of the paper making it hydrophobic allowing concentration of analytes upon evaporation make the proposed inkjet-printed SERS substrate highly promising for practical applications.

Cellulose

Nanocellulose fiber (NCF) has more excellent properties than paper, such as larger specific surface area, which enables NCF to adsorb more AgNPs. Song's group as well as Chen's team constructed flexible SERS substrates using the same approach (Song, Zhang, et al. 2021; Chen, Huang, and Kong 2020), respectively. The former deposited AuNPs on the NCF, presented a large-area flexible AuNP/NCF SERS substrate (Song, Zhang, et al. 2021). The latter constructed the NCF porous network structure on which AgNPs were grown in situ. After that, the obtained SERS chip has excellent stability (Chen, Huang, and Kong 2020). The experiments of Jiang and Hsieh demonstrated that the cellulose nanofibril (CNF) surface bound Ag nanoprisms were easily prepared as freestanding CNF/Ag nanoprisms films, resulting in R6G showing excellent SERS with an analytical EF of 5×10^3, while the CNF/Ag nanospheres films did not (Jiang and Hsieh 2014). Overcoming the uniformity of filter paper, a new type of paper fluid sensor is created, enabling quantitative analysis of SERS sensors. The raw material preparation process is shown in Figure 9D, which describes the two measurement methods of the sensor (Lin, Yu, et al. 2020). Jeon et al. deposited gold nanorods (AuNRs) or silver nanowires (AgNWs) on regenerated cellulose (RC) to detect microplastics, and found that the AgNWs/RC SERS substrate had better activity through experimental comparison (Jeon et al. 2021). AgNWs-coated oxidized CNF surfaces were applied for conducting electrodes. After the dense anisotropic porous AuNPs were deposited on the surface of the electrode (Figure 9B), the R6G was detected, and the EF was as high as 8.71×10^{11} (Kim, Kim, et al. 2021). In addition, the detection limit of other gas phase or liquid phase detection, is also very low, while the sensitivity is extremely high.

Nanocrystalline cellulose (NCC), obtained by cellulose acid hydrolysis, is considered as an important nanocellulose for its high crystallinity and mechanical strength, and the presence of NCC can improve the thermal stability of the material and act as a stabilizer for AgNPs (Ogundare and van Zyl, 2019). Ogundare and Van Zyl established the application of NCC (isolated from discarded cigarette filters) as a dual reducing agent and stabilizer in the synthesis of AgNPs. The potential of the formed AgNPs as SERS substrates for the detection of fluorescent analytes (riboflavin) at μM concentration levels was demonstrated (Ogundare and van Zyl 2018). Subsequently, their group also achieved the amplification of the SERS "hot spot" by clustering NCC-reduced AgNPs with the assistance of silica nanoparticles. The substrate exhibited higher sensitivity and higher signal enhancement in the detection of MG compared to

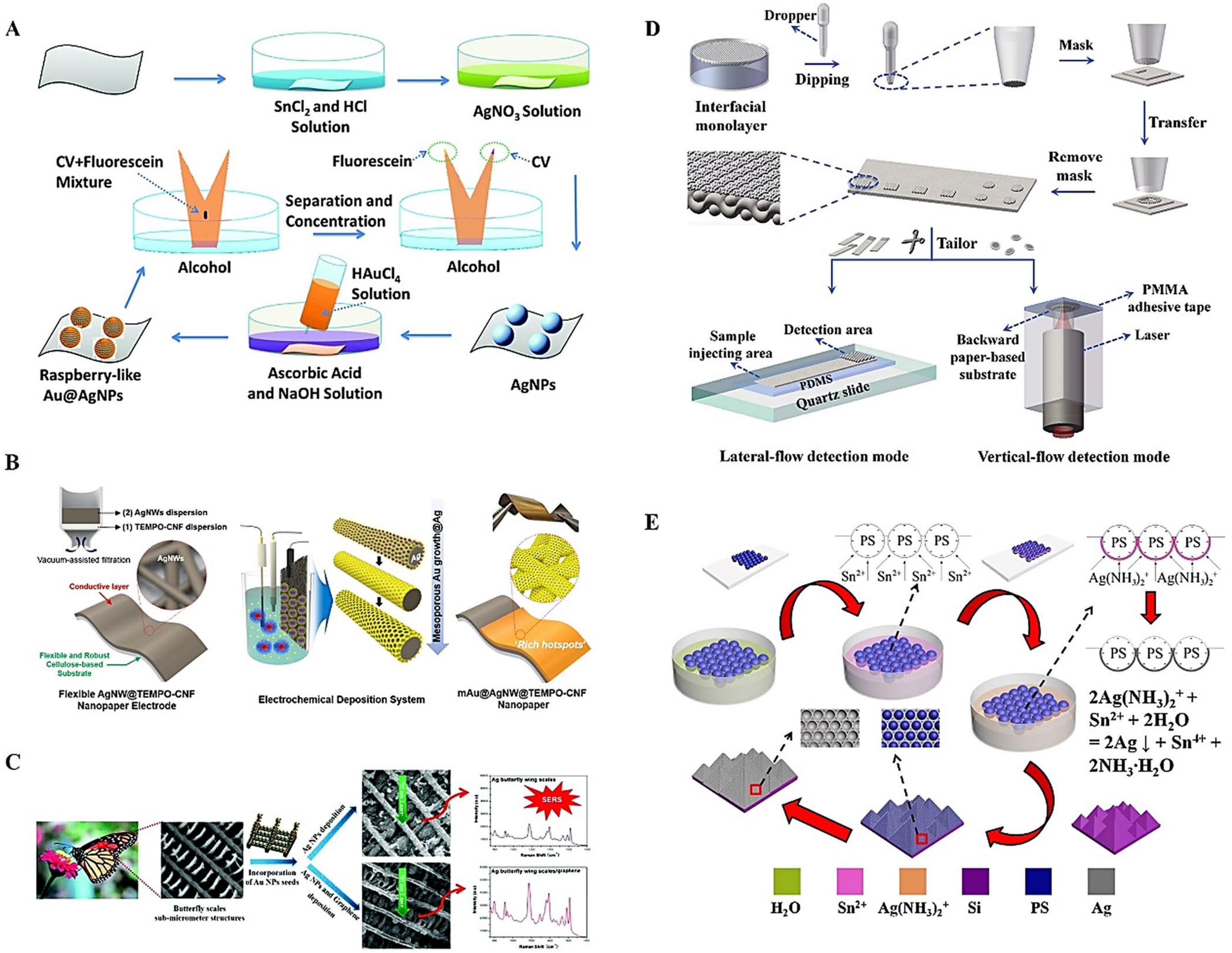

Figure 9. Schematic illustration of A) the fabrication and application process of raspberry-shaped Au@AgNPs/paper substrates and B) the preparation scheme of mAu@AgNW@TEMPO-CNF nanopaper. Reproduced with permission (Xu, Ding, et al. 2021). Copyright 2021, Royal Society of Chemistry. Reproduced with permission (Kim, Kim, et al. 2021). Copyright 2021, Elsevier B.V. C) Schematic illustration and characterization of the fabrication process of 3D Ag butterfly-wing scale arrays/graphene composites as 3D SERS substrates. Reproduced with permission (Zhang, Huang, et al. 2018). Copyright 2018, Royal Society of Chemistry. D) Schematic illustration of flexible approach to fabricate uniform monolayers of Au@4-MBA@Ag NSs colloidal on the filter paper for lateral-flow and vertical-flow detection modes. Reproduced with permission (Lin, Yu, et al. 2020). Copyright 2020, Elsevier B.V. E) Schematic illustration and principles of the preparation process for 3D bio-inspired anti-reflective SERS substrate. Reproduced with permission (Li, Chen, et al. 2021). Copyright 2021, Elsevier B.V.

the silica-free NCC-AgNPs substrate (Ogundare and van Zyl, 2019).

AuNPs-modified cellulose filter paper SERS substrates were prepared without the addition of reducing agents by Linh et al. (2019). AuNPs were grown directly on polymerized dopamine (PD)-coated cellulose filter paper by a simple solution impregnation method. The size of the synthesized AuNPs was adjusted by varying the pH of the gold precursor solution and it was found that the particles with an average particle size of 102 nm formed under acidic conditions showed the best SERS activity (Linh et al. 2019). A simple, low-cost method was used to for polydopamine-mediated self-assembly using DNA as a template and silver-modified cellulose nanofiber composites (Xu, Ding, et al. 2021). This approach has been shown to prepare 3D flexible substrates possessing high stability and sensitivity to SERS signals. Moreover, owing to the hydrogen bonding and electrostatic interactions between nanocellulose and polydopamine, polydopamine leads to the formation of a coating on the surface of rod-structured nanofibers. Adjusting the pH of the analyte to optimize the detection conditions, a linear response was obtained between SERS signal intensity and logarithmic concentration, demonstrating the promise of thiamethoxam for quantitative detection and revealing a promising future in rapid trace detection of organic contaminants (Xu, Ding, et al. 2021).

The flexibility and softness of silk allows it to be in close contact with the curved surface of skin, tissues, or organs and therefore has become an ideal material for the design and integration of high-performance biosensing platforms. Choi et al. were the first to develop a SERS detection platform by combining Au nano-islands and biological silk templates (Choi et al. 2022), and the silk-based platform is flexible, smooth, durable, and transparent, as well as the constructed nanoislands have good spatial homogeneity and rich nanogap structures, the sensitivity and spatial reproducibility of this flexible substrate are ensured. The 3D bimetal Au@AgNPs embedded on the surface of the paper (Figure 9A) was first realized by Xu, Ding, et al. (2021). The paper adopts an arrow shape, the 3D raspberry-like bimetal structure and the "tip effect" to maximize the detection effect of the SERS substrate prepared by this green process. Since the hot spots of paper-based SERS substrates are prone to uneven distribution, their signal spatial uniformity is low. Chen and his colleagues developed a nanocellulose paper-based SERS multiwell plate with high signal uniformity, and tested the SERS performance of two Raman markers, RhB and 2-naphthalenethiol, with enhancement factors up to 1.46×10^9 (Chen, Ying, et al. 2019).

Bacterial nanofibers are a natural cellulose with high specific surface area and unique mechanical strength. Through a simple silver mirror reaction, Huo et al. obtained an ideal 3D flexible AgNPs@BNC substrate, which not only detected rapidly after drying, but also had a detection limit of 10^{-12} M (Huo et al. 2020). Parnsubsakul et al. prepared an environmentally friendly AgNP-BNC paper owing to the biodegradability of BNC and performed rapid detection of pesticides on the peel by a simple vacuum filtration method (Parnsubsakul et al. 2020). AgNPs directly adhered to the 3D network nanofibrous structure of BNC paper, which exhibited good signal uniformity and SERS activity as evaluated by 4-ATP molecule. ATS was used as a coupling agent to connect AgNPs to cotton. The detection limit of melamine was 0.2 ppm for this flexible cotton swab, which was reproducible and portable. In addition, Huang et al. also successfully developed a chemical analysis APP application software that can realize instant transmission processing (Huang, Cheng, and Shyu 2022). However, the defect of this swab is a disposable product, which is not friendly to the environment. If we can study the recycling in this direction in the future, there will definitely be great development. Cellulose fibers from waste paper were recycled as support material, and AgNPs were surface-modified by electrostatic interaction for SERS detection of bisphenol A (BPA) in water and soft drinks with a sensitivity of 50 ppb (Liu, Yang, et al. 2020). This indicates that the performance of this flexible SERS is not only superior, but also beneficial to the environment, which is a sustainable development strategy.

Biomimetic material/biomimicked structured

Biomimicry refers to the science of imitating biological construction technology devices, mainly to study the structure, function and working principle of organisms, and apply them to engineering technology. In recent years, the emergence of biomimicry has promoted the rapid development of functional materials, including the development of micro-nano-level biomimicry, and biomimetic synthesis has developed as another interesting fabrication method for preparing SERS substrates. For example, by removing the PS of the gold-decorated PS spheres on the silicon micro-cone surface, a 3D silver nano-bowl-like biomimetic insect-like compound eye structure can be easily obtained (Li, Chen, et al. 2021), the construction process is shown in Figure 9E. The excellent light absorber silicon micro-cone and biomimetic silver structure greatly enhanced the SERS signal intensity. During the qualitative and quantitative detection of Hg^{2+}, it was found that the biomimetic substrate has strong anti-interference ability, and the detection limit of Hg^{2+} was 10^{-11} M (Li, Chen, et al. 2021).

Furthermore, some special micro/nano structures cannot be prepared by normal methods, while natural organisms have unique surface-variable structures. Kumar et al. used the micro- and nano-scale protrusions or bumps of taro leaves as templates, and then fabricated the hydrophobicity of the polymer to prepare a SERS sensor with a detection limit of 10^{-11} M for MG solution (Kumar, Khosla, et al. 2017). Eggshell membranes are waste or garbage to us, but some scholars use them to build flexible SERS substrates to study the pesticide residues of thiabendazole (TBZ) in oolong tea (Ding et al. 2019). Based on nanoimprinting of PDMS substrates and magnetron sputtering of AgNPs, Sun and colleagues replicated multifunctional flexible bionic SERS substrates with different surface structures from four different agricultural products, lettuce, cucumber, carrot and cantaloupe (Sun et al. 2022). After establishing standard linear calibration, smart interactive SERS assays were also performed to investigate the advantages of these bionic substrates for in situ SERS measurements on different surfaces. Successfully, recoveries of more than 80% were obtained in all cases, which demonstrated the robust and practical SERS detection capability of the prepared bionic substrates. More importantly, the recovery rate was highest when the surface of a certain agricultural product served as a template for the assay (Sun et al. 2022). We can be reasonably confident that a highly consistent sampling surface can significantly improve the capture efficiency of the substrate for the target molecules.

AuNPs@cicada wings can also be recycled by simple $NaBH_4$ washing (Lv et al. 2015). The well-known biomimetic recognition polymers have the characteristics of high specificity and high stability, and the sensor formed by combining with the previously mentioned cellulose paper base has become an important tool for pesticide detection (Liu, Zhao, et al. 2022). Shi's research team used lotus leaves (Shi et al. 2018) and Wang et al. used dragonfly wings (Wang et al. 2018) as biological templates. After sputtering AgNPs, they both presented an island-like SERS active substrate. On this basis, Yan et al. sputtered a copper layer to fabricate a sandwich structure in the form of Ag@Cu@cicada wing (Yan et al. 2019). The added metal layer results in a higher density of hot spots in the whole system, an increase in detection sensitivity and a lower detection limit. A layer of AgNPs was deposited on the surface of Ag@Cicada wing, and the detection signal was remarkably enhanced after the surface was roughened (Wang, Le-The, et al. 2020). Furthermore, the cicada wing is a natural environment. In addition to being a natural template, it can also satisfy the in situ culture of bacteria and realize the monitoring of endotoxin (Xiang et al. 2020). The initial array of chitin-based scales on butterfly wings provided a new biological fold. A simple and efficient approach based on biomimetic synthesis was reported to prepare 3D butterfly wing scale arrays/graphene hybrid substrates as actual SERS substrates (Zhang, Huang, et al. 2018). Different dimensions of graphene and AgNPs decorated on the butterfly wings are used to achieve 3D substrates by the simultaneous reduction process (Figure 9C). The novel 3D Ag butterfly wing array/graphene composites are subsequently cut into pieces as SERS substrates for direct detection of various target analytes, which demonstrate the great potential for rapid in situ sensing.

Inorganic material

Semiconductor material

Since the report in 2011, MXenes, as a new class of 2D materials, have attracted extensive attention at home and abroad, and have become a hot research topic due to their unique physical and chemical properties. Hybridization of metal nanoparticles onto MXene nanosheets broadens the surface plasmon resonance band and has a higher detection sensitivity for methyl blue (Satheeshkumar et al. 2016). The outbreak of the new coronavirus in 2019 is still threatening the health of human beings around the world. The research on the SARS-CoV-2 virus is very urgent and has never stopped. Nucleic acid detection has also become a necessary work for medical care. Therefore, efficient and rapid nucleic acid detection technology has become the research direction of many researchers. Using semiconductor materials to prepare SERS substrates, Peng et al. reported the SERS enhancement of Nb_2C and Ta_2C MXenes for the first time, and found that the substrates prepared by Ta_2C MXenes has the ability to sensitively and accurately identify the SARS-CoV-2 spike protein (Peng et al. 2021).

The differences in the mechanism of semiconductor TiO_2 and common noble metal Ag as active SERS substrates were investigated by Jiang, Zou, et al. (2018). Novel 2D amorphous TiO_2 nanosheets were developed, the high electronic density of states and small band gap increased the resonant coupling, and the activity of the nonmetal SERS substrate was also more obvious (Wang, Sun, et al. 2019). Keshavarz et al. realized the quantum-scale structure of TiO_x and used it directly on the SERS substrate, eliminating the need for noble metal decoration. Induced the formation of atomic-level defects in TiO_x, and the Raman signal was also prominently improved (Keshavarz et al. 2020). Hydrogenation is an effective method to improve the SERS performance of semiconducting TiO_2, which can improve its EF by at least 3 orders of magnitude. Yang et al. successfully integrated ultrasensitive active SERS with self-cleaning properties on black TiO_2 NWs substrates by hydro-processing (Yang, Peng, et al. 2018). Gu and his colleagues also summarized the preparation methods of molybdenum oxides, the mechanism and properties of molybdenum oxides used as SERS, etc (Gu, Li, et al. 2021)., which provides a great reference for everyone to understand the substrate of semiconductor-based oxide SERS. Currently, Xie's team combined two approaches to design TiO_2@MoO_x nanoheterojunctions from TiO_2@MoO_x nanorods and analyzed the SERS enhancement mechanism in detail through the energy band spectra of the two oxides. Under a 532-nm laser irradiation, the electron-hole pairs was separated, and the free electrons moved toward the MoO_x surface and finally transferred to the Raman reporter molecule (Xie, Lai, et al. 2022).

However, the enhancement mechanism of the PS/Cu_2S/Ag sandwich structure innovated by Xue et al. can also be attributed to the synergistic effect of EM and CM, the strength is naturally high, and the method of magnetron sputtering is simple and effective (Xue et al. 2022). Because the dual boosts of EM caused by LSPR and CM caused by interfacial CT act on WO_2 dendrites, and the SERS chip prepared by WO_2 nanodendrites had high uniformity, the activity of this new substrate was no worse than that of noble metal substrate (Ye et al. 2020). For SERS substrates prepared from semiconductor materials, the photoinduced charge transfer rate is the key. The study found that temperature has an effect on porous ZnO nanosheets, the photoluminescence intensity of the porous ZnO nanosheets increased at low temperature, which effectively promoted the charge transfer between the substrate and the molecule in the SERS system and improved the activity (Lin, Yu, et al. 2020).

Since most noble metal substrates are expensive, semiconductor substrates are low cost but somewhat less efficient. Zhang et al. modified an appropriate amount of AuNPs on the ZnO nanocap, which not only saved the cost, but also had a very broad application prospect of the SERS substrate (Zhang, Peng, et al. 2020). Tran et al. fabricated CuO nanowires with a one-step method, with uniform texture and lengths of 3–5 μm and diameters of 100 nm (Tran et al. 2020). When the charge was transferred from the silver layer to the CuO layer, the surface plasmon resonance was enhanced. The $Cu_{2-x}S$ ultrananoparticles formed by Zhang et al. have stable performance and high SERS enhancement, and the detected analyte concentration could be as low as 10^{-8} M. Copper sulfide semiconductors have good antibacterial properties, which inspires that ultrananoparticles can be used for in situ detection of bacterial killing processes (Zhang, Chen, et al. 2022). As a non-precious metal substrate for SERS, MoO_2 nanocrystals could be used to detect a range of high-risk compounds, such as BPA and PCP. It broken through the long-standing barrier of metal oxide application in SERS and truly enabled the preparation and application of highly sensitive, stable and versatile non-precious metal-based SERS substrate materials (Zhang, Li, et al. 2017).

The enhancement of many semiconductor materials mainly comes from the high SERS activity caused by charge transfer, while the activity of the novel SERS substrate based on MoO_2 nanosheets reported by Xu et al. mainly comes from the SPR effect, and reducing the thickness can also properly enhance the Raman signal (Wu, Chen, et al. 2018). More importantly, the nanosheet has high stability and can be reused. MoO_2 nanomaterials exhibit superior SERS performance because of their low resistivity and high free electron concentration. Ren et al. investigated the important contribution of surface topography to molybdenum oxide SERS. The MoO_3/MoO_2 nanosheets were synthesized by oxidizing MoO_2 nanosheets (Ren, Zhou, et al. 2020). Due to the tip effect, a strong electric field enhancement is formed in the crevices of the corrugated MoO_3 NSs, indicating that the surface morphology has a great influence on the SERS signal. 2D transition metal telluride (TMT) could efficiently enrich the adsorbed probe molecules and produced significant CM (Tao et al. 2021). More importantly, the low-symmetry atomic structure of 1T' TMT enabled its high surface activity, which ensured strong interactions between the analyte-TMT interface, leading to coupling of EM enhancement and CM in the plasmonics-TMT hybrid structure. In the study of Tao et al., the facile and high-throughput preparation of the AuNPs-$MoTe_2$ hybrid structure as a high-performance SERS medium was reported (Tao et al. 2021).

Carbon-based nanomaterials

In recent years, carbon-based materials have attracted extensive research interest due to their good mechanical properties, structural stability, and chemisorption properties. Pérez et al. used chemical vapor deposition-obtained graphene material instead of polymer to transfer metal nanoparticles, and thus, the heterojunctions were free of impurities (Pérez et al. 2016). Moreover, after annealing, the surface metal formed various morphologies, such as triangular or circular nanoplates, which enable the detection of SERS and TERS with excellent sensitivity. Nevertheless, Sun and his two partners reported the structure of PMMA/AgNPs/graphene (Sun, Liu, et al. 2017). PMMA maintains the flexibility of the substrate, AgNPs realizes LSPR, graphene avoids the contamination of the sample and can also adsorb pesticide residues in the aqueous phase. This appropriate combination has the characteristics of green reusability and has great potential in practical applications. Wang et al. revealed the SERS enhancement mechanism of graphene/AgNPs hybrid system, where graphene as an electron reservoir provides electrons, which are transferred to the metal layer to realize plasmonic excitation (Wang, Zhu, et al. 2017). Kim et al. studied the effects of graphene and hexagonal boron nitride (h-BN) on SERS substrates from two aspects: long-term stability and different electrical properties. Excitingly, the stability of SERS substrates using 2D monolayer h-BN film remained more than 80 days, better than graphene (Kim et al. 2019). The 2D plasmonic matrix was rapidly deposited by spraying an appropriate amount of air-jet AgNWs colloidal solution on a thin graphene paper (G-paper) (Amicucci et al. 2021), using G-paper to host the NPs deposition, providing a flat background and superior reproducibility. The detected droplets are applied to the surface layer, and they are directly used for detection after drying.

Furthermore, Graphene oxide (GO) still maintains the layered structure of graphene, but many oxygenated functional groups are introduced into the graphene monolith of each layer, and it has a large specific surface area, which effectively prevents agglomeration. Krishnan and Godoy collaborated to design a 3D controllable GO/Au NS hybrid composite structure, which has abundant "hot spots" and good reproducibility and stability in application (Krishnan and Godoy 2020). Using multiple layers of GO as spacers, 3D SERS substrates with different numbers of AgNP layers were prepared, and the four-layer strength was found to reach an extreme value (Li, Wang, et al. 2018). The double enhancement of SERS substrate was realized by hybridizing noble metal nanoparticles with graphene on the surface of porous gallium nitride (GaN), and finally the selective quantitative detection of Pb^{2+} was carried out by the principle of enzyme-linked reaction (He, Wu, et al. 2021). Choi et al. successfully developed a highly sensitive and selective graphene oxide (GO)-hybrid SERS array to monitor dopamine (DA) secretion at the single-cell level. DA-specific detection can be achieved by binding malachite green-labeled aptamers to the surface of the SERS array (Choi et al. 2020). Typically, Ag/GO composite inks are spin-cast on rigid glass substrates. The Ag/GO films were densified by steps such as high temperature spinning and baking, followed by a simple "stick and peel" using commercial tapes (Choi et al. 2017). This low-cost tape is easy to process, and its adhesive side serves as a convenient instrument for transferring and supporting Ag/GO films. This is a simple method to fabricate flexible SERS tapes, and its excellent signal reproducibility with 1.3% RSD confirmed this as an efficient substrate fabrication method (Choi et al. 2017).

Expanded graphite (EG) is a highly porous material with a worm-like structure, with a large specific surface area, relatively low cost, and the ability to be compressed without the use of any binder. A 3D porous EG SERS platform was fabricated with AgNPs as modified materials, which provided the elimination of the coffee ring effect and fast solvent penetration into the matrix, enabling one to perform fast SERS measurements (Çelik and Kurt 2021). Yan et al. used reduced graphene oxide (rGO) membrane prepared by the filtration method and found that the Raman signal intensity of the R6G molecule on the membrane was related to the thermal reduction temperature, and the rGO membrane obtained at 800 °C had the best performance (Yan et al. 2017). Moreover, the shape and thickness of rGO paper-like film are controllable, the cost is low, and the preparation method is simple. Wu et al. investigated the SERS enhancement mechanism of MoS_2 quantum dot/rGO substrates and found that the large enhancement of SERS signal is due to the CT formed at the interface of 1 T phase between organic molecules and MoS_2 QD with small-sized ultrathin flakes and the chemical enhancement of rGO (Wu, Chen, et al. 2018).

Oxidized carbon cloth (OCC) as a metal-free, low-cost and flexible SERS substrate candidate. Meng et al. demonstrated theoretically and experimentally that the introduction of oxygen-rich functional groups by chemical oxidation on the surface of OCC enhanced the CT between the OCC and the Raman reporter and enhanced its SERS activity (Meng, Shang, et al. 2022). In addition to graphene's excellent electron transport layer, carbon nanotubes (CNTs) with special electrical and chemical properties are also ideal for active SERS substrates. Zhang et al. prepared CNTs/AgNPs hybrid materials, and selected the 2D Raman peak of CNTs as the internal standard, and the signal homogeneity was improved (Jie et al. 2018). Just like the stronger Raman signal of Au@Ag core-shell NPs mentioned in "Metal Nanoparticles," Tian et al. dispersed the Au@Ag core-shell NPs they have reported on CNTs to maintain high density, which facilitates the electron-photon coupling of CNTs and can provide an ultra-low detection limit of 10 fM (Tian, Zhang, et al. 2019).

In summary, this section introduces the main material sources for constructing flexible SERS substrates, which can be mainly divided into reinforcing materials and supporting materials. Table 1 summarizes the detailed comparison of substrates built on different materials including substrate structure, design strategy, sensitivity (LOD), flexibility/superiority, and application. By comparison, it seems that the sensitivity of the reported SERS substrates is relatively high, but the application of flexible materials is relatively extensive, and the reproducibility and stability are relatively good. Thin and rigid brittle products are not conducive to production storage and application, while most flexible SERS are capable of tensile strain testing within a reasonable range, and for this reason, it is believed that companies prefer to prepare flexible detectors into commercial products. From the literature listed in Table 1, it can be found that flexible substrates are widely used in food safety, biosensing, environmental detection and medical health due to their unique properties, which we will also discuss in the next section.

Functional applications of flexible SERS substrates

Flexible SERS substrates are capable of being wrapped around complex sample surfaces for in situ SERS detection or real-time monitoring. They have tremendous application prospects in food safety, biosensing, medical diagnostics, environmental contamination detection, and cell culture. In this section, we review the recent research status in these related fields and demonstrate the significance of flexible SERS substrates. Table 2 summarizes the representative results of the flexible SERS substrates. It can be seen that these flexible substrates possess excellent detection sensitivity (10^{-9}–10^{-13} M), and some of them can even be reduced to the single molecule detection level.

Food safety

It is often said that food is the priority of the people, safety is the minimum requirement for food consumption. Without safety, the color, aroma, and nutrition are impossible to talk about. Safety is also the highest requirement of food consumption, which is related to the health and even life of the people, and food safety is the overriding factor. Nowadays, with the rapid development of commodity industrialization, large-scale food productions can be completed in a short period of time. While pursuing high efficiency, many food safety accidents have occurred. Such as pesticide and veterinary drug residues, illegal addition of additives or even toxic and harmful substances, or long-term storage that causes food spoilage and mildew to be detected. Nevertheless, if the relevant testing departments or consumers can use scientific and effective methods to conduct serious testing on various types of food, they can fundamentally ensure the safety of food hygiene. The flexible SERS substrate is easy to wrap or wipe sampling on non-planar surfaces, providing convenience in nondestructive detection of food (Zhang, Chen, et al. 2021). The SERS technology has huge applications in food safety detection due to its convenience, high sensitivity, rapid response, and in-situ detection. Cui et al. directly wrapped the AuNP-AgNWP SERS active substrate on the surface of lemon, and the in-situ detection of pesticide residues could be reduced to 72 ng/cm^2, which is far lower than the food safety allowable (Cui et al. 2017). Xie et al. briefly described the application of SERS to various pathogens and analytes in food matrices and the correlation of SERS substrate types with food samples. Jiang et al. discussed its application status in the detection of pesticides, microorganisms, antibiotics, metal ions and other food poisons (Xie, Pu, and Sun 2018; Jiang, He, et al. 2021).

Synthetic dyes have been widely used in food processing, but the use of pigments in food needs to be appropriate. Once abused, it will cause serious harm to human health. The novel coccine and orange II in paprika and Melinda soft drinks were studied by SERS technique, achieving rapid and sensitive determination (Wu et al. 2020). Sun et al. synthesized a light-weight, low-cost SERS template to detect the illegal food additives Basic Orange II and RhB in pepper products with detection limits of 0.5 and 0.1 μg/mL, respectively, and also achieved mixed check. The detection mechanism is analyzed by density functional theory, which provide a research reference for related similar detection (Sun, Li, Hu, et al. 2021). Wang et al. developed a novel SERS sensor for the detection of kanamycin in food with a detection limit of 3.03×10^{-13} g mL^{-1} under optimized detection conditions (Wang, Sun, et al. 2021). The sensor exploits an aptamer-controlled switch, catalytic properties of Zn-doped CQDs, and plasmonics of size-controllable AuNRs to enhance the SERS signal. The sensor has good specificity, high sensitivity and wide linear detection range for the detection and quantification of kanamycin, and has been successfully applied to the detection of kanamycin in honey and milk. Moreover, the sensor can be easily adapted to detect other harmful substances in food by simply changing the sequence of the nucleic acid aptamer (Wang, Sun, et al. 2021). The flexible SERS chip reported by Wang et al. was used to detect TBZ residues in fruit juices with long-term storage stability and low detection line (ppb level) (Wang, Sun, et al. 2019). Furthermore, the preparation process of the chip is simple and easy to operate, which provides a potential possibility for the development of portable flexible wearable sensors.

Heavy metals in the human body will interfere with the transport of human proteins and enzymes, causing great harm to the human body. Guo et al. introduced the progress of SERS in the detection of heavy metals such as mercury, arsenic, cadmium, chromium and lead in food and agricultural products (Figure 10A) (Guo et al. 2021). Lead ions (Pb^{2+}) are toxic heavy metals that are extremely harmful to human health and the environment. Using DNAzyme-modified Fe_3O_4@Au@Ag nanoparticles (Fe_3O_4@Au@Ag NPs), Xu et al. developed a facile and high-sensitivity SERS biosensor for the selective detection of Pb^{2+} with a detection limit of 5 pM

Table 1. A detailed comparison of substrates built on different materials including design strategies, performance advantages, and applications.

Substrate	Design strategy	Sensitivity (LOD)	Flexibility/superiority	Application	Ref
Au-coated TiO_2 nanotube array	Photocatalytic deposition and hydrothermal method	1.0×10^{-9} M (herbicide 4-chlorophenol)	Highly sensitive, stable, reproducible	Continuous monitoring	Li et al. 2010
MoS_2 decorated with AuNPs/Si-NSHs (nanosquare holes)	E-beam lithography	10^{-11} M(R6G)	High efficiency and sensitivity	N.A	Ko and Chen 2022
TiO_2/Ag LROCs (Long-Range Ordered Crystals)	Colloidal lithography techniques	10^{-7} M (RhB)	Self-cleaning	Photocatalysis	Korcoban et al. 2022
Au triangular nanogap arrays	Molecular self-Assembly, colloidal nanosphere lithography, and physical peeling	1 pM (MB) and 100 pM (adenine)	Templated, reproducible, and high-throughput	N.A	Luo et al. 2022
Au nanotriangles (AuNTs)	Seed-mediated overgrowth	10^{-8}–10^{-9} M (4-mercaptobenzoic acid and benzyl dimethylammonium chloride), 1–10 nM (BDA^+)	High sensitivity	SERS sensing	Kuttner et al. 2018
Ag mirror/Au nanorings/Ag cover sandwich nanofilm	Self-assembly and Langmuir-Blodgett techniques	N.A	More hot spots in z-axis	Molecular recognition and detection	Zhang, Peng, et al. 2020
Ag/MoO_3-coated PS template	Self-assembly and cosputtering	N.A	Opens up a new horizon for the study of SERS in oxygen-containing semiconductors	To offer a reference for future studies of SERS in oxygen-containing semiconductors and new band assignments for PATP	Chu et al. 2021
AgNPs@GO/PET	Dip-coating method	N.A	10–20 cycles with no significant loss in the catalytic activity	Catalytic reduction of organic pollutants	Sharma et al. 2022
hexagonal-packed Ag-coated silicon nanorods array	Self-Assembly	10^{-14} M(TNT)	Incomparable uniformity and reproducibility	Molecule trapping and SERS sensing for organic molecules	Song et al. 2022
Au@DFH-4T@NP-PDMS	Thermal evaporation	10^{-10} M (vitamin D3, cholecalciferol)	Exhibited acceptable efficiency and durability after 100 cycles bending tests, decreased 60% after the 250 cycles	Diagnosing chronic kidney disease	Wang, Xu, et al. 2022
GO/Ag/SiO_2/Au/Si	Self-Assembly, nanosphere lithography technique, spin-coating	10^{-9} M (melamine)	Low-cost, and large-area fabrication	Food safety control and environmental monitoring	Wang, Xu, et al. 2022
4-inch Si wafer-scale graphene-nanopyramids hybrid SERS system	Colloidal lithography, modern semiconductor nanofabrication process	10^{-10} M (R6G, MB, catalase and lysozyme)	Large scale, highly uniform, and sensitive	Label-free detection of chemicals, proteins and cells	Wu, Niu, Ren, Jiang, et al. 2022
AgNP/PMMA	A drop and peel-off technique	4.24×10^{-8} M (parathion) and 2.74×10^{-9} M (fenitrothion)	Bending and torsion up to 50 cycles; good spot-to-spot uniformity and batch-to-batch reproducibility	In-situ SERS detection on curved fruit/vegetable surfaces	Wang, Sun, et al. 2021
AuNPs/polyvinyl chloride (PVC) film	One-step interfacial self-assembly	10 ng cm^{-2} (thiram)	Good reliability, outstanding stability and reusability	On-site and in situ multi-pesticide residue detection, food safety and environmental monitoring	Wu, Luo, et al. 2019
PMMA/paraffin/graphene	Colloidal lithography and a modern semiconductor nanofabrication process	10^{-11} M (R6G)	Graphene on AuNPs shows tensile strain	Catalysis, biosensors, light-emitting diodes, solar cells, and advanced transparent conductors.	Wu, Niu, Ren, Jiang, et al. 2022
3D Au@PDMS	Self-Assembly	6.3×10^{-10} M(thiram)	Good flexibility and accuracy, optical transparency, the recovery rate of about 98.7% to 104.9%	On-site detection of pesticide residues	Xie, Lai, et al. 2022

(Continued)

Table 1. (Continued)

Substrate	Design strategy	Sensitivity (LOD)	Flexibility/superiority	Application	Ref
Graphene/Ag-nanoflowers/PMMA	Graphene templated micro-current-assisted chemical reduction method	10^{-14} M (R6G), 10^{-11} M (phenylalanine, adenosine aqueous, MB)	Low-cost, quantity production and easy to pack, handle and discard after use to avoid cross-contamination	Quantitative determination	Qiu et al. 2017
AuNS-embedded PDMS films	Self-Assembly	10^{-8} M (benzenethiol)	SERS sensors maintain the high sensitivity even after mechanical deformations of stretching, bending, and torsion for 100 cycles	Various SERS sensing applications, chemical imaging, direct and nondestructive for observation of samples	Park, Lee, and Ko 2017
Ordered metallic sub-micrometer pillars arrays	Anodic aluminum oxide templates	N.A	A facile and cost-effective strategy to fabricate highly ordered metallic nanoarrays	N.A	Xiang et al. 2022
Au@PDMS nanofiber	Electrospinning	10 nM (R6G and ascorbic acid)	No appreciable change after 1000 stretching cycles (50% strain), easy-to-fabricate, low-cost, ultrathin, flexible, stretchable, adhesive	Food safety, environmental monitoring and infection surveillance, the sensor for the detection of sweat biomarkers, drugs of abuse, and microplastics	Liu, Zhao, et al. 2022
3D Ag metalized nanotrenches	Nanoimprint lithography	10 pM (CV)	N.A	Developing optical biosensors	Colniță et al. 2022
$Ag_{nano}@Cu_{NPS}$	Chemical etching, Electro-displacement Reactions	1.7 pg/mL (Creatinine)	Low cost and wide availability of brass, the simplicity of the procedure	Point of care diagnostic	Sajitha et al. 2021
MCA (microsphere cavity array)/AuNPs/PDMS	N.A	10^{-10} M (4-NBT), 2.42 ng/cm^2 (thiram)	Constant Raman intensity for up to 20 folding-bending cycles	Wearable devices	Wang, Xu, et al. 2022
Bipyramid-AuNPs based SERS tape	Seed growth method	ng/cm^2 level (R6G and CV)	A new versatile sensing platform	To monitor a trace number of chemical hazards for food and agricultural safety	Wu, Luo, et al. 2019
Au nanodendrites decorated microwells on conductive tape	Physical punching, magnetron sputtering and electrochemical deposition	10^{-12} M (R6G)	Good storage stability, almost unchanged Raman intensity after two weeks	Food safety, forensic, military, consumer protection, and environmental monitoring	He, Yang, et al. 2020
AgNPs@ZnO-nanorods/PAN-nanopillar arrays	Template-assisted synthetic, electrochemical depositing	10^{-13} M (R6G) , 10^{-8} M (parathion-methyl)	Self-cleaning, high reusability (retain stable SERS sensitivity after 5 cycles)	Detection of trace organic pollutants in the environment	Tang et al. 2018

Table 2. Partial comparison of SERS substrates for non-flexible substrates and flexible materials for analysis of practical applications.

Material structure	Characteristics	EF/sensitivity (LOD)	Raman reporter molecule/promising application	Ref
Aptamer-functionalized Au NPs array	Label-free, highly sensitive, and selective	N.A/0.8 pM	Interleukin-6 (IL-6); Medical diagnosis	Muhammad, Shao, and Huang 2021
AgNPM-AuH arrays	In situ monitoring of the surface-catalyzed conversion	$1.09\times10^9/10^{-12}$ M	R6G; contaminants, Proton-driven photocatalytic	Zhang, Chen, et al. 2021
Au-Ag alloy nanostructure	Highly dense, accessible nanogaps and uniformity, ultrasensitive	1.09×10^9/10 fM	MG; Pesticide	Lee, Kwon, and Lee 2020
N-MoS_2@AuNP	Ultrasensitive, high Reproducibility, controllable SERS hot spots	$10^4/10^{-10}$ M	RhB	Rani et al. 2020
Gyroid-structured Au periodic metallic materials	Highly sensitive, reproducible and uniform	0.8×10^9/1 fM	Bis(2-ethylhexyl) phthalate; Plasticizers for food, household products, paints, perfumes, etc.	Wu, Chen, et al. 2018
Au-coated silicon (Au@Si) dimer-nanopillar arrays	High-sensitivity and Reproducibility (3.2- 5.6%)	$4.3–8.0\times10^9$/N.A	For the detection of rapeseed oil components	Yue et al. 2020
3D Ag nanobowls/Si pyramids	Simultaneous trace detection of four common dyes	N.A/10^{-13} M	R6G、CV、MG、MB; In food	Jin et al. 2021
Au@SiO_2	Facile and low-cost, uniformity	$3.74\times10^{10}/10^{-12}$ M	R6G; Monitoring the catalytic process, photodetectors	Zhao, Xiao, et al. 2018
Sharp-tipped Au nanopyramid arrays	Sensitive, noninvasive	1×10^6/N.A	ND7/23 neuronal cells; Detecting both the membrane constituents, proteins and lipids	Iarossi et al. 2022
AuNPs@2-mercaptohydroquinone@ ZIF-8	High reproducibility, wide detection range, and favorable anti-interference ability.	N.A/0.357 nM	H_2O_2; Biosensing and early disease diagnosis associated with H_2O_2 secretion	Jiang, He, et al. 2021
MIL-100(Fe)	To simultaneously detect the different gaseous indicators of lung cancer with a ppm detection limit	10^{10}/2.5 ppM	Toluene; Diagnosis of lung cancer in vivo	Fu et al. 2020
Ag melamine thin film	Flexible, resistant, extracted and concentrated target molecules	N.A/10^{-10} M	Thiram; Food-related applications, agricultural needs, and environmental control	Nenashkina et al. 2021
AuNP micro-hemisphere PDMS film	High-density and ordered "hot spots," effectively the sensitivity and signal consistency	$9.16\times10^7/10^{-12}$ M	CV; Pesticide residues	Zhang, Li, et al. 2019
Raspberry-like bimetallic Au@ AgNPs/paper	Paper-based sensors with remarkable analysis and detection capability	N.A/1 pM	MG; The fishpond water	Xu, Ding, et al. 2021
Ag/PMMA nanocomposites	Rapid, simple, low-cost, ultrasensitive	$10^{15}/10^{-10}$ M	Trans-1,2-4 (bipyridyl) ethylene (BPE); Ultrasensitive SERS sensors	Fahes et al. 2021
GO/AgNPs/pyramid PMMA	Excellent adhesion, flexibility, high sensitivity, homogeneity and stability	$8.1\times10^9/10^{-13}$ M	R6G, MG, CV; Food safety	Xiu et al. 2018
T/Au@Ag/PET	Offering opportunities for wearable, lightweight, and flexible SERS substrates	N.A/7.24×10^{-10} M, 5 ng/cm^2	CV, thiram; Food safety analysis, environmental monitoring	Wang, Sun, et al. 2021
PMMA@Au core-shell	High stability, versatile SPR tunability, Au NPs surfaces that are more easily functionalized for bioconjugation	N.A/10^{-8} M	4-aminothiophenol (4- ATP); Environmental monitoring, food regulation and public health, disease detection	Kassim, Padmanabhan, and Pemble 2021
AuNPs@4-MPY/Ca-ALG fibers	Low-cost, versatile and flexible	N.A/1.00–13.00 pH	4-mercaptopyridine (4-MPY); Health monitoring	Zhang, Chen, et al. 2022
Periodical Au grating @polymer film	Rapid and unpretentious outdoor analysis, high reproducibility and reliability	N.A	Yeast cells; Biodetection and recognition	Kalachyova et al. 2018
Ag/Au NWs/PDMS film	Low cost and facile fabrication, utilizing the SERS peak of PDMS as intrinsic internal standard, the environment Fluctuation could be eliminated	$6.74\times10^6/3.8\times10^{-9}$ M	2-naphthalenethiol, methyl parathion (MP); Food and environmental security	Ma et al. 2020
Au@DFH-4T@NP-PDMS	Ultrasensitive, acceptable mechanical durability and SERS stability	N.A/10^{-10} M	Vitamin D3, cholecalciferol; The wearable diagnosis for biomolecules	Wang, Xu, et al. 2022
AgNPs @PET	Not require expensive equipment or processes	1.6×10^4/1 nm	R6G; For potential bio-probe or remote applications	Adewumi et al. 2022
AgNRs tape	Increased the store time of AgNRs, weakened the fluorescent background from matrix, and could probe SERS inactive surfaces, solutions and even powders.	N.A/28.8 ng·cm^{-2}	Tetramethylthiuram disulfide; In food analysis, noninvasive identification, environmental monitoring	Jiang, Zhao, et al. 2019
AuNB-PDMS hybrid film	Good flexibility, reliable transparency, and promising SERS performance	$2.56\times10^6/1\times10^{-10}$ M	4-nitrothiophenol (4NTP); In food and environmental protection	Ma et al. 2021
FP@PDA@AgNPs strips	High sensitivity and excellent reproducibility, to fabricate a variety of flexible, cheap and portable SERS sensors	N.A/10^{-10} M	R6G; Surface contamination analysis, the environmental scientific analysis and food safety monitoring fields	Zhang, Peng, et al. 2020

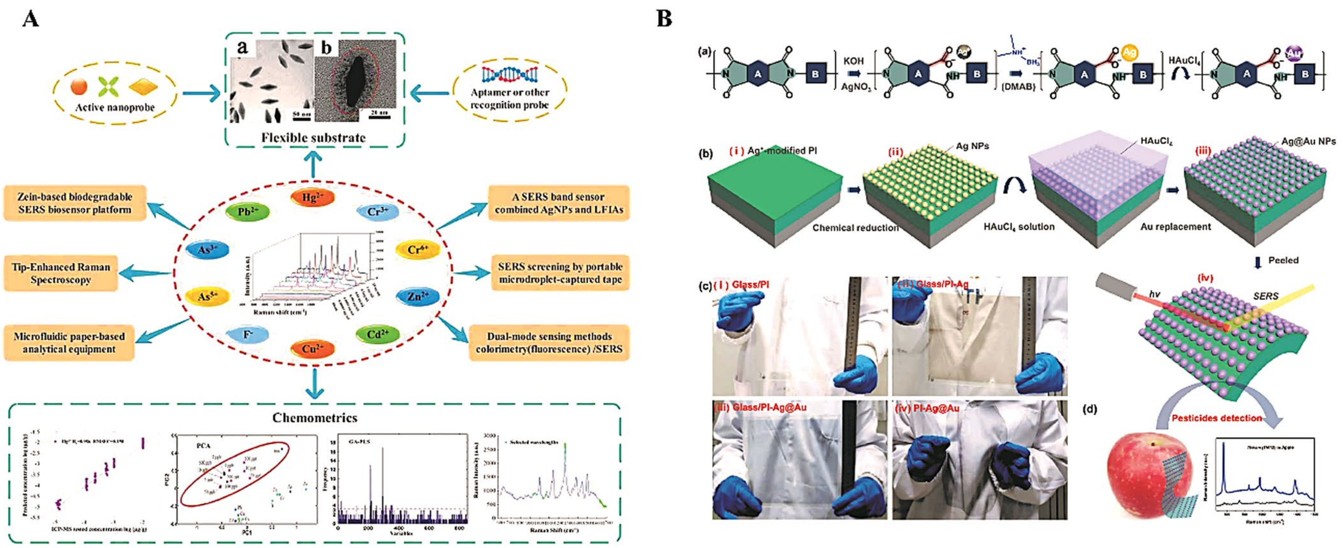

Figure 10. A. Schematic application of SERS technology for heavy metal detection in food and agricultural products with flexible substrates and chemometrics. Reproduced with permission (Guo et al. 2021). Copyright 2021, Taylor and Francis Ltd. B. (a) Schematic of Ag@Au NP growth and (b) corresponding flexible SERS sensor fabrication, (c) photograph of the fabrication process of a large area SERS sensor ($20\times20\,cm^2$), (d) direct sampling and SERS detection map of pesticides on apples. Reproduced with permission (Liu, Yang, et al. 2020). Copyright 2020, American Chemical Society.

for Pb^{2+} (Xu et al. 2020). It also provides ideas and strategies for the design and detection of SERS biosensors for other heavy metal ions.

Commercial tapes with good transparency and extraction ability could be used as collectors, and AgNR@Al_2O_3 serves as a uniform and sensitive SERS substrate for rapid detection of analytes in real environments (Jiang, Zou, et al. 2018). Qualitative detection of tetramethythiuram disulfide (TMTD) and TBZ pesticide residues in apples, cucumbers, pears and spinach was carried out (Jiang, Zou, et al. 2018). The proposed T-SERS strategy is a convenient and versatile method that could be used to detect various analytes from specific surfaces or complexes. The sensitive detection of molecules was achieved by the particle/molecule/film (POF) sandwich configuration of Wang, Zhu, et al. (2017). In the SERS assay, the Au film could be in close contact with the fruit surface to extract pesticide residues due to the low background noise of the flexible tape. The final pesticide molecule is well confined to the hot spot region of the assembled POF structure allowing the maximum possible SERS signal of the pesticide molecule to be obtained (Wang, Zhu, et al. 2017). Chen and colleagues modified commercial tapes with colloidal AuNPs to construct novel substrates that possess both SERS activity and the "sticky" of the adhesive. The utility of SERS tape is demonstrated by a simple and feasible "paste and peel" method for the direct extraction of pesticide residues in vegetables and fruits. Obtaining strong and easily identifiable SERS signals facilitate the detection of multiple pesticide residues in complex surface samples such as real green vegetables and common fruits (Chen et al. 2016).

Liu et al. took samples directly from the surface of apples to fast track the residues of the pesticide TMTD with a sensitivity of $10\,ng/cm^2$ (Figure 10B) (Liu, Yang, et al. 2020). Due to the good adhesion of SERS-active substrates, it is very suitable for on-site sampling and real-time detection. Thiram is widely used as a plant fungicide, which is toxic and can cause harm to humans when it remains in crops or the environment. The detection results of the flexible SERS film prepared by Yang et al. for MG detection on fish surface and thiram detection on orange peel were 1×10^{-10} M and 1×10^{-6} M, respectively, which is lower than the national standard requirements (Yang, Peng, et al. 2018). Similarly, Alyami et al. obtained AgNPs/PDMS composites through self-assembly, it is also used to detect fish skins and orange peels. The in-situ detection of irregular objects can be directly realized by using the "stickiness" of the substrate (Alyami, Quinn, and Iacopino 2019). Au nanoisland films (AuNIFs) with tunable island morphologies were fabricated by wet-chemical method by Khlebtsov et al. Reproducible SERS-active substrates based on AuNIFs detect thiram on apple peels at levels of $5\,ng/cm^2$ (Khlebtsov et al. 2015).

Flexible fluorinated ethylene propylene (FEP) surface plasmon resonance membranes were fabricated by one-step femtosecond laser-induced plasma-assisted ablation for in situ detection (Xu, Ding, et al. 2021). The nanoparticles produced by the femtosecond laser are much smaller, and the effective tuning of the laser fluence can optimize the density and size distribution of AuNPs or AgNPs on FEP films. The prepared substrate can be used for high-sensitivity in situ SERS detection of trace pesticide residues on fruit peels (Xu, Ding, et al. 2021). Besides, rapid and accurate detection of pathogenic bacteria is a hot research topic in the field of food safety and public health. Liu et al. overviewed recent advances in label-based and label-free bacterial SERS detection methods, including bacterial SERS profiling and novel multifunctional detection platforms (Liu et al. 2017). It also pointed out that SERS technology has challenges in multiple labeling, complex sample detection, and standardization of operating procedures. Qu et al. overviewed the application of SERS technology in the rapid detection of food-borne bacteria and viruses in food matrices in recent decades, and found that SERS-based methods can achieve high sensitivity and specificity (Qu et al. 2021).

The indirect SERS immunosensing platform has the advantages of high specificity, good sensitivity and stability in the quantitative analysis of amantadine (AMD) in animal-derived foods, and can be used for rapid screening of foods where AMD is a contaminated component (Yang, Pan, et al. 2021). Chien et al. analyzed five kinds of edible pigments in commercial candy with the help of SERS sensor made of alumina beads, and the response was good (Chien, Chang, and Huang 2022). Moreover, the sensor is easy to prepare on a large scale, convenient and effective to use, and importantly, can be arranged in a matrix for automation, which is especially suitable for programmed automatic detection. In the past ten years, people have paid more and more attention to the nutritional value of food. Radu et al. used SERS technology to simultaneously detect two B vitamins (vitamin B2, riboflavin and vitamin B12) (Radu et al. 2016). Antibiotic residues in food have become one of the core issues of food safety. Therefore, rapid and effective analysis methods must be adopted to prevent these residues from entering our body. Reasonable detection technology is very important. Liang et al. comprehensively reviewed the latest progress and advancements of SERS in the detection of antibiotic residues (Liang, Peng, et al. 2021). Furthermore, if necessary, the future SERS system can be combined with other detection methods, which will accelerate the application of SERS technology in the field of food safety and quality.

Biosensor

Currently developed biosensing methods generally use enzyme-linked immunosorbent assay (ELISA) or polymerase chain reaction (PCR), but their wide application in POC (point-of-care) diagnosis is due to low specificity and low sensitivity, limited by the inability to differentiate between low concentrations of pathogens and live/dead bacteria. However, SERS biosensors are naturally a superior choice due to their ultra-sensitive, relatively low-cost, fast, and reusable properties. Kim et al. introduced a label-free cellulose SERS biosensor chip for the identification of subarachnoid hemorrhage-induced cerebral vasospasm and cerebrospinal fluid-induced cerebral water (Kim et al. 2018). Moreover, in order to improve the LSPR effect of AuNPs, the pH-adjusted cellulose surface is further functionalized, and the final EF of the biosensor is 3.29×10^9 (Kim et al. 2018). Liang et al. reviewed the recent research progress of SERS sensors for the detection of bioactive molecules, especially the design, fabrication, basic principles of operation, and biological applications of carbon-based SERS biosensors (Liang, Peng, et al. 2021). It also provides its own insights into the development of a new generation of SERS biosensors. Some scholars have also proposed that flexible plasmonic biosensors can be developed in five emerging fields (Song, Zhang, et al. 2021), integrating traditional dimensions into large-scale sensors; developing biosensors based on physical sensing mechanisms of conductivity and spectroscopy; innovating sensors with biocompatibility and degradability; exploring flexible sensors to prioritize public health interventions as well as incorporating smart technologies to enable different users to obtain clinical feedback as needed.

The SERS activity of Au Cu/GO reported by Li et al. is regulated by DNA, which is both sequence- and length-dependent, and short polyT has the strongest ability to enhance SERS activity. The SERS biosensor can detect APEI sensitively and selectively, making it promising for clinical application (Li, Heng, et al. 2019). Credi et al. designed a novel fiber-cap sensor that reversibly converts the inert tip of a fiber-optic photonic system into a SERS substrate, improving the sensitivity of molecular detection in liquid samples. The SERS test and fluorescence image results show that the biosensor has a stronger affinity for amyloid-β than the bare sensor without ligand (Credi et al. 2020). To achieve sensitive and reliable SERS detection, an innovative core-Raman molecule-shell-shell (C-M-S-S) SERS nanoprobe was designed (Dai et al. 2020). The outer shell is made of a responsive switch, which can respond quickly and realize the SERS signal sensing process of living cells. The SERS probe has the characteristics of high sensitivity, good selectivity, fast response and high reproducibility for the detection of GSH. Clear ratio cell imaging of GSH in live cells is also possible. Additionally, the nanoprobe could also detect the accurate degradation efficiency of MnO_2 shell materials (Dai et al. 2020). BPA is an organic chemical material, but it is a typical environmental hormone. Long-term low-dose intake will cause damage to the human nervous system and endocrine system, and even cause cancer. Zhang et al. detected BPA in water via a BPA-specific SERS tag with high specificity and accuracy (Zhang, Chen, et al. 2022).

Signal DNA (sDNA) and 4-MBA were assembled on the surface of AgNCs, and a SERS biosensing platform for the preparation of AgNCs/sDNA/4-MBA was proposed. The heated electrode promote nicked endonuclease-assisted signal amplification, enabling highly sensitive detection of oral cancer-related DNA species (Liu, Guo, et al. 2021). Aptamers are the only single-stranded DNA/RNA sequences that can specifically recognize and capture target analytes (Xiao et al. 2019). Combined with SERS technology, multiplex detection can be achieved. Muhammad et al. reviewed the detection principles, salient features (specificity and sensitivity), advantages, and limitations of aptamer-based SERS biosensors and their detection methods (Muhammad and Huang 2021). Moreover, they realized a label-free biosensor for detecting the important cytokine interleukin-6 (IL-6) in inflammation and cancer progression using the aptamer-functionalized AuNPs array as the active SERS biosensor (Muhammad, Shao, and Huang 2021). The novel SERS biosensing platform provides significant SERS enhancement through virtue of the tip effect generated by the sharp features of the edges and corners of AuNCs, showing high sensitivity in detecting DNA adenine methylation Methyltransferase enzyme activity. The detection limit of this method is 8.65×10^{-5} U mL^{-1}, which is lower than that of most sensors in the literature for the detection of this substance.

With the continuous improvement of medical equipment and the continuous adeptness and innovation of treatment technology, people's life expectancy is gradually extending. However, in addition to treatment after illness, daily health monitoring is also crucial to prevent problems before they occur. The analysis of sweat pH is very helpful for monitoring and diagnosing human physiological health. Chung et al. used electrospinning to prepare nanofiber-active SERS substrates, which responded well to 4-MBA and 4-MPy (Chung et al. 2021). Moreover, the SERS pH sensor prepared with this chip has good resolution, and the sensor concept is described in Figure 11A. KoH and his team developed a wearable SERS patch-type biosensor containing a skin-contacting sweat-absorbent layer and a SERS-active layer that protects against damage and pollution (Koh et al. 2021). This is a nondestructive and label-free method, and the SERS patch also has excellent skin biocompatibility and flexibility, which is expected to be applied to wearable medical devices.

Hydrogen peroxide (H_2O_2) is widely involved in intracellular and extracellular redox signaling pathways and plays a considerable role in regulating various physiological events, but current H_2O_2 analysis methods are often hindered by long response times or self-interference. Therefore, Jiang and his colleagues developed a ZIF-8-based SERS sensor by depositing ZIF-8 on SERS-active AuNPs bearing the H_2O_2-responsive probe molecule 2-mercaptohydroquinone, and detected the H_2O_2 released by cells (Jiang, He, et al. 2021). Combined with the efficient enrichment and selective response of ZIF to H_2O_2, the ZIF-8-based SERS sensor has superior anti-interference ability and excellent detection sensitivity for the detection of H_2O_2.

The flexible nanopatches reported by Durai et al. were used for the SERS detection of biomolecules (ascorbic acid and uric acid) and metabolites (glucose, lactate) in human sweat (Durai and Badhulika 2022), showing high stability, reproducibility, selectivity and excellent performance in the detection process, making it promising for wearable biodetectors. The electrically modulated SERS substrate constructed by Xu et al. was used for flexible wearable biosensors to detect lactate content in runners' sweat (Xu, Ding, et al. 2021). The fabricated flexible wearable SF-AAO-Au sensor exhibits excellent SERS mechanical flexibility, sensitivity, biocompatibility, and good mechanical flexibility (deformation within 5%). It can be used to detect glucose in human sweat, or it can be designed as a SERS sensor glove for laboratory use to detect pesticide residues. The prepared SERS-active composite fibers were pH-dependent and woven into a wearable "wristband" for real-time detection and continuous health monitoring (Zhang, Chen, et al. 2022). At present, sensors mainly rely on enzymes or antibodies as biological recognition molecules to achieve specific quantification of metabolites and stress biomarkers in sweat. However, enzymes and antibodies tend to degrade over time, affecting sensor performance. Mogera et al. report a plasmonic paper-based wearable microfluidic system for continuous and simultaneous quantification of sweat rate metabolites and losses (Figure 11B) (Mogera et al. 2022). The wearable plasmonic device is flexible, soft, stretchable, and can be in solid contact with the skin without chemical or physical irritation.

Medical diagnostics

MicroRNAs (miRs) are small noncoding RNAs used to regulate mRNA stability or translation. Due to the remarkable stability of miRs in the circulation, miR levels in biological fluids can be used as biomarkers for the diagnosis and prognosis of diseases. Joshi's paper is the first to describe the use of gold nanoprisms to detect miRs in patient plasmonics (Joshi et al. 2014), manifesting high sensitivity and selectivity, and strong practicality. Shao et al. introduced a multiplex signal amplification sandwich SERS biosensor for the detection of miRNAs. Benefiting from the advantages of this structure, the detection limit of ultra-trace miRNA-141 is very low at only 0.03 fM (Shao et al. 2019). Therefore, this biosensor with facile preparation and multiple signal amplification has broad application in clinical cancer diagnosis. The continuous advancement of medical technology has made the requirements for detection methods and detection times higher and higher. Among them, the SERS detection technology satisfies the requirement of the improvement speed very well. With the advent of handheld Raman technology, Raman tests can be performed anywhere, anytime, with immediate results, exhibiting the advantages of this technology, including improved diagnostic accuracy, reduced diagnostic costs, and improved diagnostic efficiency. Liu et al. summarized the research progress and clinical application of SERS technology for point-of-care diagnostics in biochemical sensing (Liu, Guo, et al. 2021) and Granger et al. reviewed the potential impact of SERS in addressing the unmet need for pathogen diagnostics in conventional clinical settings and point-of-care areas, and also highlighted various applications of the SERS technology (Granger et al. 2016). Song proposed a novel SPR/SERS bimodal biosensor based on catalytic hairpin assembly (CHA)-induced AuNP network for the highly sensitive and specific detection of cancer-related miRNA-652 in human serum (Song, Zhang, et al. 2021). The dual-SERS biosensor of Pang et al. achieves the identification of microRNAs with a detection limit of 1 aM in one-step (Pang et al. 2019).

Nanostructures with good internal nanogap can provide highly uniform and stable SERS signals. Li et al. proposed label-free Au@Ag AuNPs active SERS for cancer cell imaging and multiplex quantitative detection. This method eliminates the need for sulfurized DNA, is low cost and time consuming without sacrificing sensitivity and reproducibility (Li et al. 2016). Zhang et al. realized multiple quantitative detection of cardiac biomarkers based on SERS technology for early diagnosis of acute myocardial infarction (Zhang, Huang, et al. 2018). Ag-Au core-shell bimetallic nanotags with Nile blue A (NBA) encapsulated in an internal gap between the two metals (Ag^{NBA}@Au) were used in place of Au colloids in the conjugate pad as shown in Figure 11C. Detection antibodies for each of the three biomarkers Myo, cTnI, and CK-MB were conjugated to

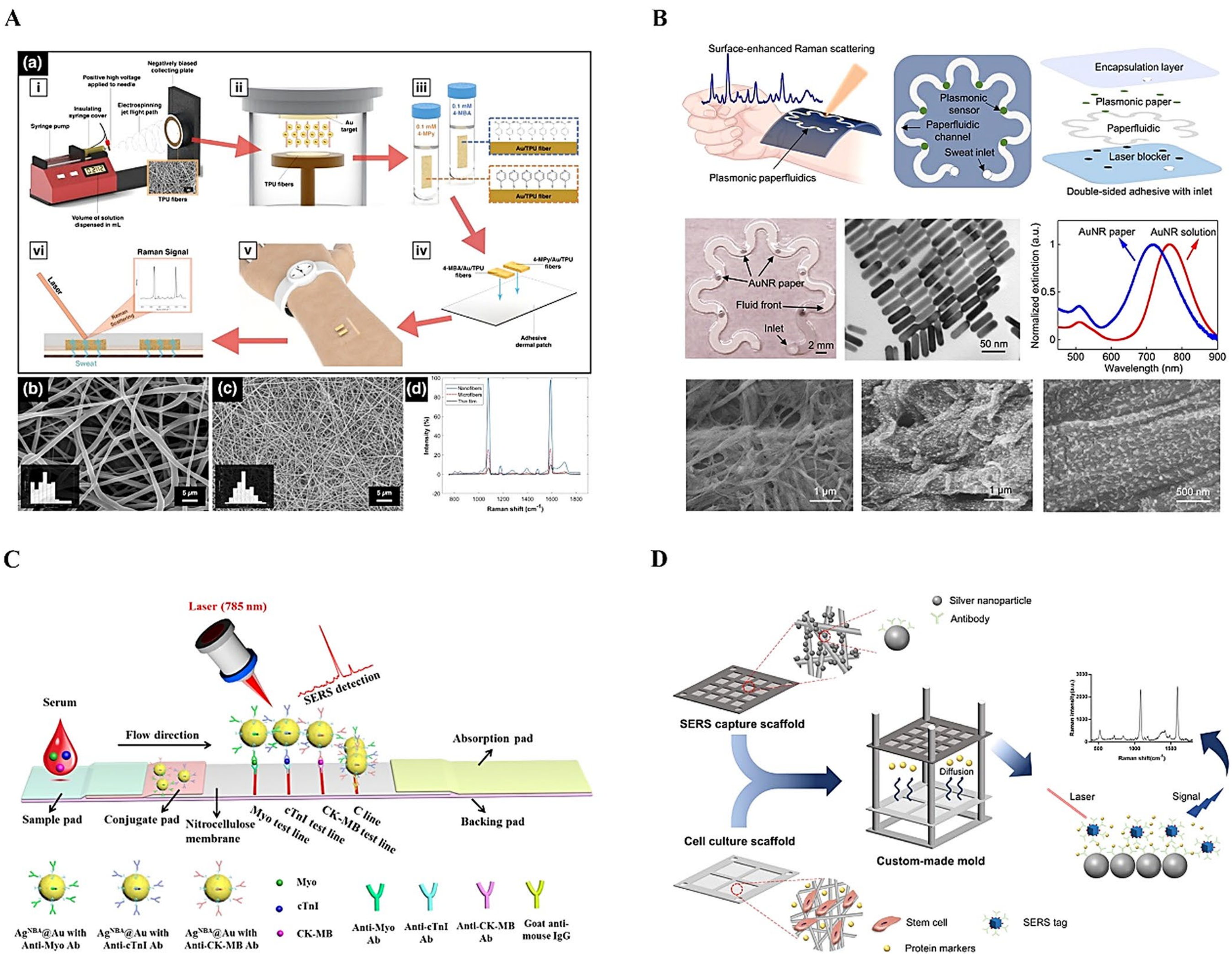

Figure 11. A. (a) Fabrication steps of pH-responsive SERS-active Au/TPU electrospun fiber nanofiber wearable patch, SEM image of electrospun TPU 18% w/v with (b) no additive and (c) added HCl, (d) Raman signal intensity comparison of 4-MBA/Au on TPU film and TPU nanofibers, and microfibers without added HCl. Reproduced with permission (Chung et al. 2021). Copyright 2021, American Chemical Society. B. Schematic diagram, physical diagram and various characterizations of the fabrication principle of the wearable mass spectrometry paper microfluidic device. Reproduced under terms of the CC-BY license (Mogera et al. 2022). Copyright 2022, the Author's. Published by AAAS. C. Schematic illustration of the Ag-Au core-shell SERS nanotag-based multiplex lateral flow assay. Reproduced with permission (Zhang, Huang, et al. 2018). Copyright 2018, Elsevier B.V. D. Schematic illustration of integrating SERS-based biosensors and 3D cell culture scaffolds to detect protein markers secreted by stem cells. Reproduced with permission (Ko et al. 2021). Copyright 2021, Elsevier B.V.

SERS nanotags and three test lines were prepared on nitrocellulose membranes for multiplex detection. After sample is flowing from the sample pad to the absorber pad, the Raman signals of the three test lines are measured to quantify the cardiac biomarkers (Zhang, Huang, et al. 2018). The ultra-sensitive lateral flow assay with a wide linear dynamic range is achieved thanks to the high specific surface area to volume ratio of the porous cellulose membrane and the strong signal of the SERS nanomarker. Bhamidipati et al. examined the cancer biomarker epithelial cell adhesion molecule (EpCAM). In particular, real-time tracking of cancer tissue evolution can be achieved by monitoring small changes in the expression of targeted EpCAM (Bhamidipati et al. 2018).

Zhao et al. obtained a SERS nano label integrated magnetic separation biosensor for whole blood immunoassay (Zhao et al. 2019). In addition, because lung cancer has a high mortality rate, early diagnosis can help improve prognosis. Shin et al. demonstrated that deep learning-based exosome-based SERS can accomplish accurate diagnosis of early-stage lung cancer (Shin et al. 2020). Prior to Litti et al., no SERS or Raman sensing device was able to quantify flumioxazin in water or erlotinib in human plasma. Litti et al. obtained detection limits for the diagnostic herbicide flumioxazin and the anticancer drug erlotinib using human plasma samples (Litti et al. 2021). The results demonstrate that the system has good detection capabilities for pollutants and drugs in the relevant environmental/biological range. El-Mashtoly and Gerwert briefly introduced the main Raman spectroscopy techniques and reviewed applications for biomedical diagnosis and evaluation of therapeutic candidates using different samples (El-Mashtoly and Gerwert 2022). It is clearly felt that with the development of theranostic techniques, patients progressively benefit from these rapid responsive monitoring and accurate diagnosis.

Environmental pollutant detection

Environmental pollution has long been a concern of society due to the health hazards, wide distribution and variety of pollutants. The discharge of a large amount of untreated water, gas, slag and other harmful wastes in industrial production will seriously damage the ecological balance of agriculture and natural resources, and will also pollute the environment and directly endanger the health of the general public. SO_2, industrial dust, smelting residue, plastic (Dey 2022; Hu et al. 2022), fly ash, cyanide, organic pollutants (Zhang, Xu, et al. 2016; Wei, Huang, and Vikesland 2019) and harmful heavy metals (Park et al. 2022) are all common pollutants. Zhang et al. used SERS paper to quantitatively analyze the organic pollutant benzidine and internal reference in environmental samples (Zhang, Huang, et al. 2018), and found that the recovery rate of benzidine in environmental water is 117%–140%, and the detection limit is 0.2 μM (that is 0.2 micromole). The possibility of practical application of SERS paper is also evaluated in the report. Processes such as sensing and degradation of toxic dyes can be accelerated through photochemical processes such as photoinduced catalytic degradation and SERS. Parvathi et al. investigated TiO_2/Ag/GO nanocomposite (TAG) as an ideal dual-matrix for SERS sensing and visible-light-driven degradation of Congo red and CV (Parvathi et al. 2019), which is of great significance to the green and sustainable development of the environment. The graphene nano-mesh-Ag-ZnO metal (GNMM) nanohybrid fabricated by Bharadwaj et al. could be applied to photocatalysis, antibacterial and self-cleaning SERS detection of organic pollutants (Bharadwaj et al. 2018). The synthesized GNMM nanohybrid SERS substrate has the advantages of simple preparation method, low cost, reusability, and sensitive detection, and has great application prospects in the application of antibacterial drugs and detection of various environmental pollutants.

In the detection of pollutants in actual sewage, the analytes are often dispersed in inhomogeneous solutions, resulting in inaccurate Raman signal acquisition. Liu et al. fabricated SERS substrates with controllable wettability, enabling heterogeneous solutions to achieve self-separated and adsorbed in two diametrically opposite ways (Liu, Yang, et al. 2020). Similarly, Vassalini et al. also studied the detection and degradation of contaminants in water. However, this is a multifunctional water treatment system capable of simultaneously adsorbing, detecting and degrading organic pollutants. Multifunctional plasmonic hydrogels are proposed, consisting of β-cyclodextrin-functionalized AgNPs embedded in alginate vesicles. The system utilizes the LSPR of AgNPs, the affinity of β-cyclodextrin for aromatic groups, and the adsorption capacity of alginate hydrogel to achieve basic detection and environmental protection (Vassalini et al. 2020). Improper handling of uranium as the main raw material for nuclear reactors will cause great environmental pollution and ultimately harm human beings. The AgNR SERS tape was placed on the analyzed solution, and UO_2^{2+} was adsorbed on AgNR due to the strong interaction between them, thus realizing the rapid in situ detection of UO_2^{2+} (Jiang, Zhao, et al. 2019). He et al. designed flexible DNA hydrogel SERS-active biofilms as a sensor for UO_2^{2+} ion detection. Moreover, the flexible sensor exhibits good detection performance, the LOD for UO_2^{2+} is 8.38×10^{-13} M, and the selectivity for UO_2^{2+} ions is better than other 15 metal ions, representing good selectivity (He, Yang, et al. 2020).

Environmental monitoring places high demands on in-situ sensitivity to pollutants. The SERS spectra of organic molecules (MB) obtained in the plasmonic microfluidic system of Zhang et al. had high sensitivity and good reproducibility (Zhang, Li, et al. 2019). It is shown that the combination of microfluidic technology and SERS technology not only explores the field of plasmonics, but also can be used for environmental monitoring. Polychlorinated biphenyls (PCBs) are a series of toxic chemicals that are widely spread in the environment and may accumulate in humans and even cause cancer. Therefore, SiO_2@Au nanorod array was prepared by Hou et al. to detect 5 μg/g PCBs in soil samples, demonstrating its potential to detect trace environmental pollutants (Hou et al. 2015). Wang et al. systematically described various forms of detection or degradation methods and proposed SERS techniques for environmental pollutant detection (Wang, Le-The, et al. 2020). Reports indicate that direct adsorption is the simplest method for analytes that cannot form covalent bonds but are hydrophobic or contain benzene rings, including pesticides, polychlorinated biphenyls, and polycyclic aromatic hydrocarbons. Direct adsorption is the easiest way. Additionally, analytes or SERS substrates can be functionalized by boronic acid affinity, hydrophobic functional groups, and MIPs to achieve stronger and more effective affinity between the analytes and SERS substrates. HKUST-1, as a typical MOF material, has a porous structure that is favorable for capturing target molecules, which further improves the detection signal of target molecules. The hybrid SERS-active matrix reported by Huang et al. (2021), Cu mesh/$Cu(OH)_2$@HKUST-1@Au nanorod arrays, also has promising applications in the field of pollutant detection.

Phenolic pollutants tend to persist and accumulate in the environment for long periods of time with toxic effects on humans and animals. The breakthrough is that all phenolic compounds contain a benzene ring in their structure that can act as a π-electron donor, thus allowing the development of a charge-transfer based complex located on a rough silver surface containing phenolic compounds and various π-acceptors. By introducing a thin polymer layer that immobilizes the π-acceptors on the metal surface, Eremina et al. provided the ability to analyze a variety of environmental samples that can be used in sensitive, simple and rapid in situ detection of some of the most dangerous ecotoxicants including phenol, cresol, dimethylphenol, and chlorophenols in complex and chemically diverse matrices such as freshwater and gasoline fuels (Eremina et al. 2022). The detection recoveries of furazolidone (FZD) in various water environments range from 83.9 to 111.0%. Reliable linear fits were obtained for the SERS intensity versus concentration for both MB and FZD, demonstrating the quantitative determination capability of the substrate (Sun, Li, Hu, et al. 2021). Moreover, in situ detection of FZDs in fish could also be easily performed under the interference of MG, proving that the paper-based SERS substrate has great application potential in monitoring water pollutants. A large number of AuNPs were assembled based on the photothermal effect of tapered microfibers for SERS detection of pollutants in water (Xu et al. 2022). The SERS substrate realizes the quantitative detection of thiram, R6G, pyrene and other chemical pollutant solutions, and exhibits the characteristics of high sensitivity and fast response time. Moreover, combining such microfibers with microfluidic channels in the future is expected to further improve their stability and practicality.

Cell culture

Cell culture refers to a method that simulates the in vivo environment (sterility, suitable temperature, pH and certain nutrient conditions, etc.) in vitro to make it survive, grow, reproduce and maintain its main structure and function. Monitoring the cell culture process through the SERS active substrate can monitor the safety and reliability of the cell culture process. Calvet and Ryder demonstrated combining SERS with a chemometric approach for rapid identification and monitoring of chemical changes in cell culture media under normal, cold, and dark storage conditions, and demonstrated that media aging-induced changes predominate (Calvet and Ryder 2014). Due to the strong and sharp characteristics of SERS signals, it is widely used in the analysis of biological samples, from small molecules such as amino acids and glucose to macromolecules such as DNA and proteins. In addition, SERS probes are also making breakthroughs in the detection of specific biomolecules such as DNA and proteins (Jamieson et al. 2017). Ren et al. introduced a novel cell culture platform for culturing a variety of cell lines, including cancer cells and prostate cancer cells, and normal breast cells (Ren, Zhou, et al. 2020). The experimental group demonstrate that the discrimination accuracy is close to or even higher than 90%, and the prediction accuracy of the blind test group is 100%, indicating the applicability of this unique platform.

Combining different Raman reporters into SERS tags can easily identify multiple targets. 2-naphthalenethiol (2NAT) and biphenyl-4thiol (4BPT) act as Raman reporters by covalently binding to plasmonic NPs as amplifiers to form SERS nanotags. Dorleta et al. demonstrated the ability of SERS nanotags to image 3D cells and demonstrated the imaging of a structurally complex SERS-labeled 3D fibroblast biological sample (Jimenez de Aberasturi et al. 2020). Milemska et al. reported the specifics of cell culture on SERS substrates: 5500cells/cm^2 were inoculated onto SERS substrates and transferred to a shaking incubator at 37 °C for 3–4 minutes to ensure that the cells were properly attached to the substrates. Afterwards, 1 ml of expansion medium was added to each well, again maintained at 37 °C, with 95% humidified atmosphere as well as 5% CO_2 (Milewska et al. 2019). The complete cell culture medium was changed once at regular intervals and the cell culture was terminated on day seven. Cells were washed three times with PBS and fixed for subsequent SERS measurements. Furthermore, they not only study the culture of bone-marrow-derived mesenchymal stromal cells on Au nanoisland substrates, but also use these substrates to study the applicability in subsequent SERS imaging.

Ko et al. integrated a 3D cell culture scaffold and a SERS biosensor to monitor protein markers secreted by cultured stem cells (Ko et al. 2021). The detection schematic is shown in Figure 11D. The differentiated stem cells are placed on the bottom cell culture scaffold, and the substances secreted by the stem cells are detected by the SERS capture stromal cell culture scaffold on the top. By stacking multiple capture matrices, multiple labels can be detected independently and with greater space efficiency than laterally arrayed scaffolds. Within a set time, specific capture substrates are isolated from scaffold assembly and used for quantitative SERS-based immunosensing. Furthermore, this SERS-based immunoassay can detect protein markers at pg/mL levels without interference. Cellulose fibers have a porous structure that easily mimics the structure of cells, allowing cells to adhere, proliferate, differentiate, and migrate on this type of scaffold, so paper-based cell culture is very attractive and is often used to simulate 3D cell environments, and pointed out the need to judiciously design paper-based SERS frameworks for multiplex detection of metabolites (Romo-Herrera et al. 2021). All in all, cell culture has an indispensable role for basic research, and with the advances in 3D culture, 3D cell culture models increase the possibility of their conversion into applications in which data acquisition and analysis techniques are in urgent need of development and refinement. Currently, except for SERS technology, cell imaging techniques, biosensing, and elastography are also frequently applied in the cell culture process.

Conclusions and prospects

In conclusion, this review comprehensively summarizes the recent research progress of flexible SERS substrates, mainly focuses on their construction methods, diversified material selections, and multidisciplinary frontier applications. Based on outstanding advantages of flexible SERS substrates in terms of collecting and detecting target molecules, they have a wide range of applications in fields of pesticide residues, environmental pollution, biosensors, clinical medical diagnostics, cell culture, but these are not enough, and there is an urgent need to develop and apply in more real and changeable application scenarios. Fundamentally, the research findings on diversity, richness and availability of SERS substrates can greatly promote the ability of flexible SERS to detect target molecules at ever-lower levels or even the single-molecule level, and thus improve the accuracy in practical applications.

However, our focus now is to demonstrate the true potential of SERS as an advanced analytical technique in reaching commercialization. This is a daunting task, and that is best achieved by assembling integrated teams and establishing partnerships with scientific educational institutions, statisticians, instrument and assay suite manufacturers, and other end-users to deliver on the promise and drive this goal (Granger et al. 2016). The challenges include the following core elements: (1) Formulating universal testing standards to evaluate the newly constructed SERS substrates, and update and improve them in time. (2) Designing and conducting a series of well-organized experimental verifications based on "reality" samples with good characteristics. (3) Reducing the turnaround time from sample gathering to operable results. (4) Overcoming the harsh sample testing conditions, and improving the tolerance to changes with the operating environment. (5) Improving multifunctional sensing capability for competitiveness and attractiveness. (6) Building an affordable, batch manufacturing, easy operation, fast response, accurate and reliable results portable platform and a set of supporting test suites that can friendly and universal for home end-users. The encouraging news is that some efforts are being made to perform this plan, we thus believe that the suggested new path for improvement the full-scale commercial application of SERS will be fulfilled and should foresee a bright future.

Author contributions

B.-X.W. was involved in conceptualization, writing (reviewing and editing), methodology, funding acquisition. G.D. performed data curation, analyzed the results, writing (original draft preparation). W.X. analyzed the results, discussed the data. All of the authors discussed the results and commented on the manuscript. All authors read and approved the final manuscript.

Disclosures statement

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Data availability statement

The data and material that support the findings of this study are available from the corresponding author upon reasonable request.

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