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Nanomaterial-based surface-enhanced Raman scattering spectroscopy for sensing and diagnostics of gas molecules in environment and healthcare

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The detection and identification of molecular traces in the environment as well as in the human breath are very significant for the development of a healthy society. This is extremely important from the environmental control and medical diagnostics point of view. A great deal of research is being conducted in the field of gas sensing using a variety of sensing techniques. Even though several sensing materials with low cost have been developed for sensing toxic gases with relatively high sensitivity, however, sensors suffer from certain drawbacks such as poor sensitivity at room temperature. Another fact is that traditional sensors fail to discriminate the signals of different target molecules in the case of multiplex gases. Therefore, developing a sensing tool with high sensitivity, good selectivity, and simple operation for gas detection is of great significance to environment monitoring/protection and human healthcare. In this context, the surface-enhanced Raman spectroscopy (SERS) technique has emerged as one of the promising surface sensitive techniques for the ultra-detection of various kinds of species, such as chemical and biological molecules, including environmental gaseous pollutants. SERS not only provides ultrasensitive detection of molecules but also provides fingerprints of individual gases out of the mixtures, which are very complicated in the case of traditional methods. Recent advances in the SERS technique in sensing toxic and harmful environmental gases are highlighted. Additionally, this technique has shown promising application as a gas biomarker in the human breath to detect related diseases in the human body, which has also been discussed along with its possible application in the detection of SARS-CoV-2 in the breath of COVID-19 patients. Furthermore, challenges in the application of SERS technology for gas detection in the environment and their practical implementations in air pollution control, as well as human healthcare, are addressed.

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1. Introduction

The detection and identification of some species at molecular levels in the air are important from environmental safety and

control point of view, along with other technological processes such as food safety, warfare, and medical diagnosis.^{1–5} Particularly, in the case of very toxic and harmful gases present in the surroundings affecting human health, it becomes necessary to detect and identify the molecular traces with extreme sensitivity for fast control and cure of the problem that can occur.⁶ Sometimes, even very low concentrations of toxic gases, *i.e.*, as low as part-per-billion (ppb), can be critical if inhaled for a long time.^{2,7,8}

With fast-growing modern industries and agricultural waste, there is a huge production of toxic and harmful gases such as NH₃, NO₂, NO, SO₂, and volatile organic compounds (VOCs) among others, which have adverse effects not only on the environment but also on the health of human beings.^{7,9,10} Some of the gases play a major role in damaging the natural resources in the open environment producing acid rain, photochemical smog, *etc.* Similarly, some gases,

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including smog, are toxic to the human body, creating a lot of problems, particularly related to respiratory diseases, and also affect many organs of the human body.^{11,12} Hence, these poisonous and flammable gaseous chemicals in the environment cause several diseases in the human body when exceeding a certain level. For example, NO₂ causes respiratory and cardiovascular diseases at a level higher than 1 part-per-

million (ppm), with symptoms similar to those of asthma.^{13,14} NH₃ has an adverse effect on the body, skin, and also on eyes.¹⁵ On the other hand, H₂S is another very notoriously toxic gas that can cause sudden death if a person has exposure to >700 ppm.¹⁶ It also has adverse effects on cardiovascular and neurological systems.¹⁷ Therefore, monitoring very low concentration levels of these toxic and



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harmful gases in the environment is essential for people to avoid health issues. In addition, this ultra-sensitivity detection of these toxic and harmful gases could also be exploited as a biomarker for the diagnosis of various diseases by monitoring human breath.³ This is possible by examining the exhaled gases of the patients. Breath analysis could provide a promising way to diagnose diseases by detecting traces of various gases in exhaled breath.^{3,18} For example, the presence of an abnormal level of NH_3 in exhaled air could be a sign of kidney failure. The detection of H_2 and CH_4 in the exhaled air could be an indication of intestinal diseases. Similarly, the presence of nitrogen-based oxide (NO_x) gases in the human breath provides information about respiratory diseases such as bronchial asthma, chronic cough, chronic obstructive pulmonary disease, *etc.*^{18–22}

The above discussion indicates that ultra-detection of these toxic and harmful gases in the environment as well as in human breath could be a promising way to control and improve the health issues in society. Furthermore, it could be possible by the development of high-performance gas sensors. In the past few years, there has been a growing interest in developing compact and reliable sensors for gas detection in applications for human health and environmental control.^{2,7,13–15,18,23–27} These include gas chromatography/mass spectroscopy, chemiluminescence, electrochemical, chemoresistance, laser spectroscopy, *etc.*^{10,11,14,27–30} Even though several sensing materials with a low cost have been developed for sensing toxic gases with relatively high sensitivity,^{7,9,14,15,18,31–36} sensors can present some drawbacks, such as poor sensitivity at room temperature.¹⁴ Another fact is that typical sensors detect the electrical transfer resistance upon the adsorption of analytes onto the surface of the sensing nanomaterial, and it remains challenging to discriminate the signals of target molecules from those of other gas molecules.^{14,23}

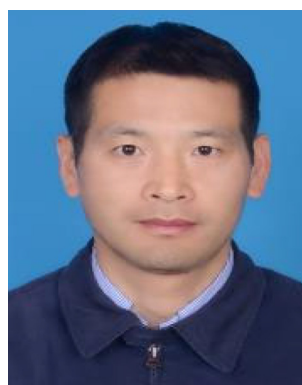
In addition to these techniques, the surface-enhanced Raman spectroscopy (SERS) technique has shown very promising application as an ultrasensitive molecular sensing tool and has the potential to increase gas sensitivity by several orders of magnitude.^{23,24,34,37–41} SERS is a promising technique for ultrasensitive detection of chemical, biological, and environmental pollutants, with the technique capable of detecting single molecules.⁴² The gas sensing response of SERS-based sensors is rapid and more reliable than that of conventional sensors, which lag behind due to limitations of low selectivity, high operation temperature, *etc.* This technique involves the application of nanomaterial-based SERS active substrates composed of noble metals^{43–45} or metal oxide semiconductors^{37,46–48} or their nanocomposites.^{40,49–51} Particularly, plasmonic noble metal nanostructures (Ag/Au) are known to be the best SERS substrates because of their unique localized surface plasmon resonance (LSPR) properties,^{39,52–55} which provide a high SERS enhancement factor (EF). Furthermore, recent advancement in synthesis and tailoring properties of plasmonic nanostructures (Au/Ag, alloys, *etc.*) has improved the molecular level sensing using the SERS technique with sensitivity limit down to sub-ppm level.⁴¹ For example, Kim *et al.*⁵⁶ developed a plasmonic-SERS-based high-performance NO_2 gas sensor with a limit of detection of 0.1 ppm that could be operated under ambient conditions. Similarly, a highly sensitive 3D Au-Ag bimetallic nanowire-based SERS sensing substrate with a high density of hot spots and strong binding between NO_2 along with a large interconnected 3D Au surface was fabricated that facilitated the adsorption of gas molecules enhancing the Raman signals. On the other hand, metal oxide semiconductors such as TiO_2 , ZnO , CuO , *etc.*^{46,48,57–60} are also used but are not so efficient as SERS substrates for ultrasensitive detection due to low SERS EF. However, these semiconductors, including 2D nanomaterials



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(i.e., GO),^{36,61–63} in combination with plasmonic nanostructures provide excellent results in SERS sensing applications.^{64–66} For example, Myoung *et al.*⁶⁷ demonstrated that Ag NPs on SiO₂ substrates could be used as a real-time vapor phase SERS detector with a detectable range of 0.6 to 800 ppm. Moreover, the SERS technique has also been used to detect different kinds of toxic gases and VOCs in the breath analysis of human beings as a gas biomarker for the diagnosis of various diseases.^{24,68–71} For example, recently, Chen *et al.*²⁴ developed SERS based approach to detect VOCs biomarkers using Au NPs and reduced graphene oxide (GO) nanocomposites in both simulated and real breath samples with ultra-sensitivity and multiplexing. This experiment provides a way to distinguish early gastric cancer (EGC) and advanced gastric cancer (AGC) patients from healthy persons by monitoring the exhaled breath samples from patients. Similarly, Fu *et al.*⁷² demonstrated that the detection of VOCs using the SERS technique could be helpful in the early diagnosis of lung cancer. The MIL-100(Fe) platform with Au NPs was employed to detect toluene and other VOCs. The limit of detection for toluene gas as a biomarker for lung cancer was found to be 0.48 ppb level with an EF of 10¹⁰.

Although researched extensively, SERS technology using functional nanomaterials with short and long-term multifunctional activities in the field of environment monitoring/control and healthcare as gas sensors has rarely been reviewed. This review provides fundamental details of SERS technology in brief, using conventional and modern portable SERS handheld spectrophotometers for point-of-care testing, which needs attention to explore for real practical applications. The emerging application of SERS technology

as a gas sensing tool for the detection of toxic and harmful gases and gas biomarkers has been discussed with an emphasis on its simple and cost effective use for the benefit of society. Furthermore, its applications in environmental control and healthcare have been explored. It is to be noted that a few reviews seem to be similar but these are entirely different because all are focused on a particular theme, either on healthcare (mainly on a particular disease or materials) or environment related (on a particular problem).^{73–78} The proposed article is focused on environmental and healthcare applications, including the pandemic COVID-19 problem and scientific solutions with a potential for commercialization because of its portability and simple handling as compared to the traditional sensor/biosensors/environmental sensors. This is an emerging research area where various plasmonic based nanomaterials and SERS technique could be potentially applied for the analysis of the human breath to monitor human health as well as for the detection of such gases in environmental monitoring, as shown schematically in Fig. 1. This review article deals with such progress in the field of SERS technique as an ultrasensitive gas sensor in environmental and multiplex gas biomarker in human health.

2. Surface-enhanced Raman scattering

As discussed above, traditional methods have been potentially used to perform qualitative analysis and quantitative detection of chemical and biological analytes; however, these are found to be somehow limited by lower

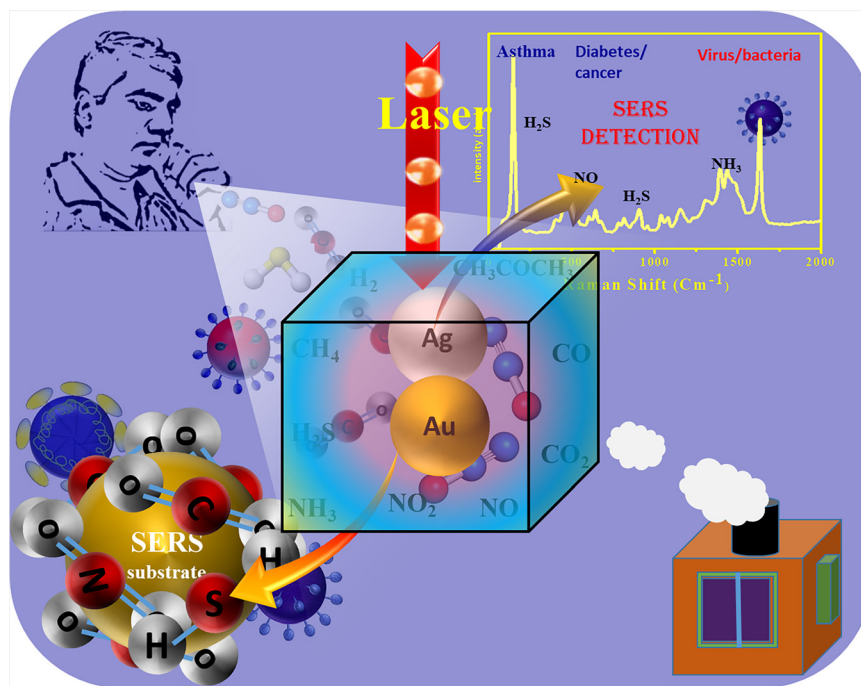


Fig. 1 Schematic of application of SERS technique (using plasmonic nanomaterials) in the analysis of the human breath to monitor human health as well as for detection of such gases in environmental monitoring.



detection sensitivity of the analytes and response time. Although there has been a lot of progress in the past decade to improve the detection sensitivity and response time, some traditional techniques are not appropriately designed to carry and are not easy to operate in the field for practical applications.⁷⁹ Therefore, research on sensing tools, which can provide high sensitivity and selectivity of the analytes along with short detection time, would be of great significance and it is the need of the day. Furthermore, the detection tool should be portable so that it can be carried anywhere for practical applications, especially when it is being used for environmental and diagnosis purposes, especially to fight a situation like the COVID-19 pandemic. In this context, SERS technology, which uses a Raman spectrophotometer, is being used as an ultrasensitive detection tool with a new spectrum detection technology. It has the potential not only to identify the fingerprints of different analytes but also to detect a lower concentration as a single molecular detection tool. Due to modern technological development in the last few years, various portable SERS tools have been invented with high sensitivity, selectivity, and rapid response, which could replace traditional sensing tools.

As discussed above, in SERS technology, SERS active substrates are used, which are generally tailored

nanostructures of noble metals, particularly Ag or Au nanostructures or hybrid nanostructures composed of noble metals with other functional nanomaterials. The unique LSPR property of the noble metals is tailored to achieve high sensitivity in the SERS technique. It is based on the enhancement of Raman scattering signals of the molecules adsorbed on the surface of nanostructured SERS active substrates when the plasmon frequency is in resonance with that of the probe radiation used in the Raman spectrophotometer.^{8,38,40,48,80} It could be explained by electromagnetic and chemical mechanisms, whereas electromagnetic SERS enhancement has been the most effective and highly acceptable.^{38,40,42,48,80}

The electromagnetic SERS mechanism is mainly due to the LSPR of noble metals, which shows a high EF due to their ease of fabrication and biocompatibility; however, there are some drawbacks when used as sole nanostructured materials in the form of powder or solutions.^{79,81} Recent developments demonstrate that surface nanoengineering of noble metal-based SERS active substrates and their composites with semiconductors provide better morphology with 'hot spot' nanoarchitectures that are suitable for higher Raman signals due to the synergetic effect of electromagnetic and chemical enhancement.^{34,48,79} It has been reported to be

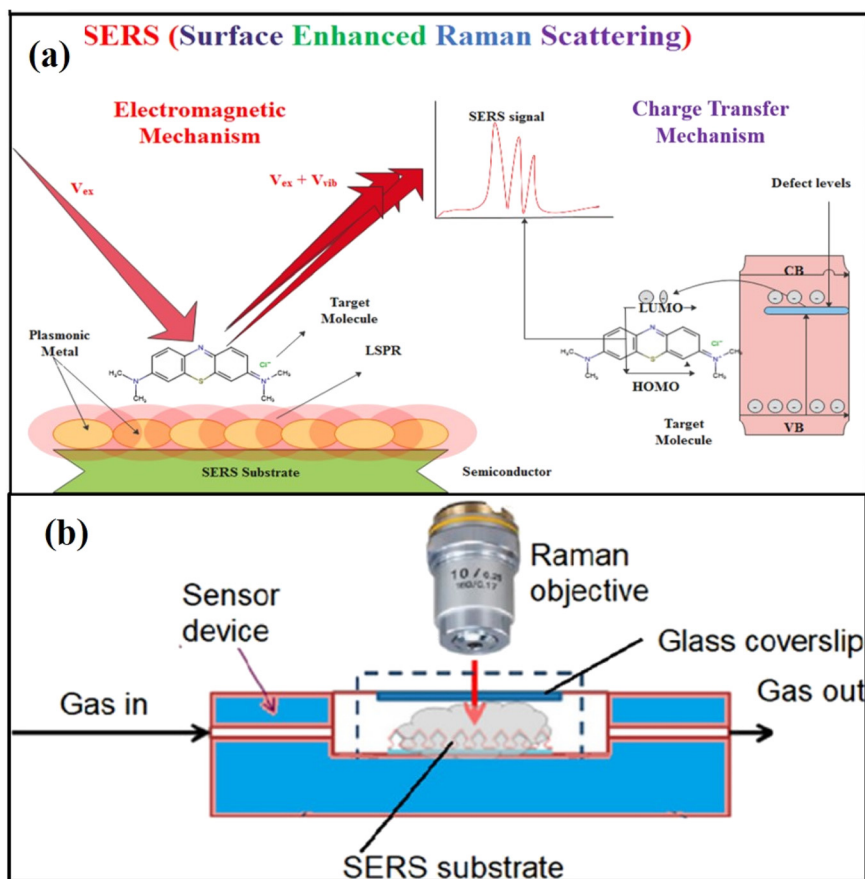


Fig. 2 Schematics of (a) SERS mechanism of electromagnetic enhancement and chemical enhancements⁸⁰ (b) experimental setup for SERS measurements in the gas phase. Reprinted with permission from ref. 2.



capable of detecting a single molecule at low concentrations of analyte molecules.⁸² SERS technique has shown its capability to detect small molecules, *i.e.*, organic pollutants, environmental gaseous molecules, ions, proteins, antibodies, nucleic acids, *etc.*^{39,47,83} along with large and complex molecules, *i.e.*, viruses, bacteria, *etc.*^{82,84–86} In the present review, the application of SERS has been described in the field of environment and healthcare as a gas sensing tool for the detection of toxic/harmful environmental gases as well as gas biomarkers in human breath. For that purpose, a set is generally designed for gas sensing using the SERS technique, as shown schematically in Fig. 2. The gaseous specimen is either used as a gas flow or collected in the chamber containing the SERS active substrates. After the analyte molecules are adsorbed on the surface of the SERS active substrate, it is kept under the focus of the laser beam from the Raman spectrophotometer, and the Raman scattering signals are collected through the detector. Similarly, it is possible to collect human breath in the analyzing chamber, and gas biomarkers can be detected. On the other hand, in the case of solid or liquid specimen sensing, no such set is required, as shown in Fig. 2. The SERS substrate adsorbed with the analyte molecules (after drying if it is in liquid) can be directly kept under the focus of the laser beam from the Raman spectrophotometer, and the SERS signals are collected. In all such cases, the SERS active substrates and their morphologies, including shape/size, play an important role in the SERS signal enhancement.

A lot of progress has been reported in the last few years in designing various 0–3D SERS active substrates using noble metals and semiconductors to enhance the EF and detect lower concentrations of analyte molecules, as discussed in the next sections, particularly in the case of detection of toxic gases and biomarkers in the environment and human breath, respectively. In addition, portable SERS devices have been developed, which are capable of several types of molecular detection in a convenient manner demonstrating as a promising candidate for point-of-care testing⁸⁷ as also discussed in the next section.

3. Application of SERS in environmental gas sensing

Due to the growing industries, agriculture, and population, the environment is full of many toxic and harmful gases, *i.e.*, CO₂, CO, NH₃, NO₂, NO, SO₂, VOCs, *etc.*,^{14,72,88–90} and these gases affect the healthy environment as well as the health of human beings. Some of the gases affect human health badly, even when present in trace amounts. As discussed above, SERS is a promising technique to detect and identify various molecular species, and several studies have reported the synthesis of tailored SERS active substrates for environmental gas sensing.

3.1 SERS detection of C, N, and S based environmental gases

As discussed in section 1, several toxic and harmful gases could be present in the environment affecting human health. The most available gases belong to C, N, and S, which have been extensively investigated. Recently, Huang *et al.*⁹¹ reported a very effective SERS substrate based on ultrathin ZIF-8 wrapped on Au-dotted Ag-nanowires (NWs) for CO₂ detection. Bontempi *et al.*⁸⁸ recently designed SiO₂/TiO₂ core/shell beads for Raman detection of environmental CO₂ under real working conditions during the solar to fuel transforming reaction. The morphology of the designed SERS substrate was tailored to trap the light for SERS resonance for enhanced sensitivity and low concentration detection of CO₂. Similarly, Yao *et al.*⁹² developed a novel SERS and resonance Rayleigh scattering (RRS) coupled di-mode method for the detection of CO using Au-based nano-enzyme catalysis as well as Au as nanoprobe. It has been demonstrated that asthma symptoms become worse when a patient is exposed to NO₂ gas between 0.10 and 0.53 ppm.⁵⁶ Kim *et al.*⁵⁶ developed a 3D nanoarchitecture-based SERS substrate composed of Au coated 1D Ag (NWs) for the detection of NO₂ gas. As shown in the scanning electron microscopy (SEM) images of Fig. 3a–c, 3D multi-layered Ag NWs of diameter 45.8 ± 6.2 nm were fabricated *via* vacuum filtration. This method produced interconnected 3D structures forming a high density of crosspoints. At the crosspoints, two NWs were closely stacked and parallel non-touching Ag NWs formed hot spots, which contributed to the SERS detection by enhancing the local electromagnetic field in the gaps due to the strong plasmonic coupling effect. Furthermore, the thick Au film was deposited onto the 3D stacked Ag NWs by sputtering the produced 3D Au–Ag bimetallic nanostructures (Fig. 3b). The average diameter of these nanostructures was estimated to be 62.6 ± 9.7 nm after depositing the 15 nm thick Au layer onto the 3D Ag NWs. The proposed SERS sensor exhibited LOD with 0.1 ppm of NO₂ along with on-site and rapid detection. It was also demonstrated that the SERS NO₂ gas sensing could be performed under ambient conditions using a handheld Raman spectrometer, as shown in Fig. 3d–f. The ultra-detection NO₂ SERS sensing was performed in vehicle exhaust tests, and high sensitivity was observed, attributed to the stable complex formation of NO₂ molecules on Au surface of than with Ag in 3D Au–Ag bimetallic nanoarchitecture. It was also proposed that this SERS substrate and a handheld Raman spectrophotometer set-up could be promising for many environmental and medical applications, including in-house air quality tests, gas sensing, and health care monitoring.

In another work, Kim *et al.*⁹³ demonstrated that similar SERS-active plasmonic chips with a 3D nanoporous architecture composed of Ag NWs deposited with Au hemispheres on their surfaces were extremely sensitive with fast NO₂ gas sensitivity at room temperature. Recently, Li *et al.*⁹⁴ studied the interaction of oxides of S and N (*i.e.*, NO₂, NO₃, SO₃, and SO₄) on plasmonic metal Ag surfaces. It was



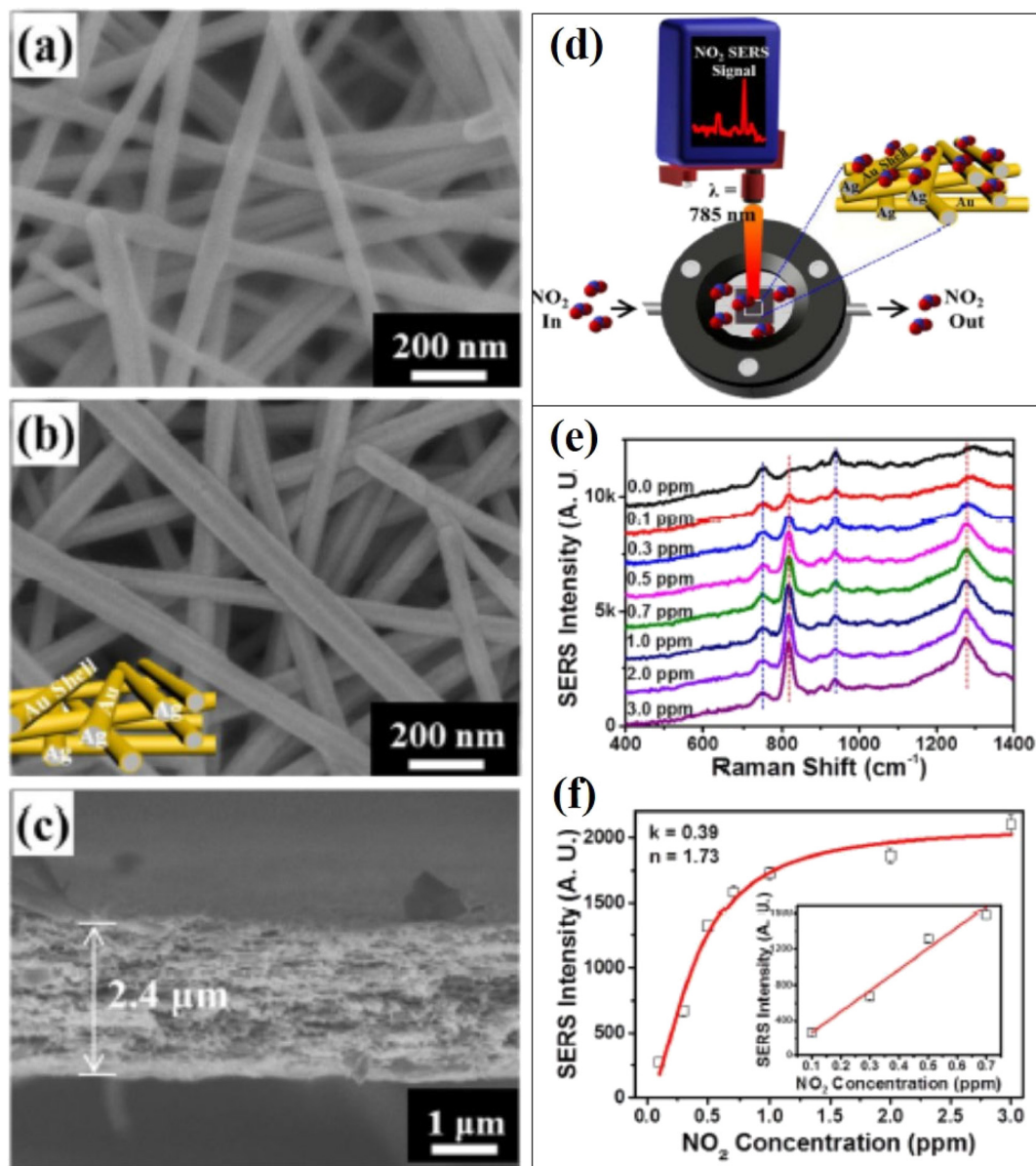


Fig. 3 SEM micrographs of 3D stacked (a) Ag nanowires (NWs) and (b) Au-coated Ag NWs. (c) X-SEM micrograph of the NWs. (d) Schematic representation of *in situ* NO₂ gas detection process under ambient conditions. (e) SERS spectra of NO₂ gas at different concentrations from 0.1 ppm to 3 ppm. (f) Calibration curve based on the SERS intensity at 810 cm⁻¹ as a function of the NO₂ gas concentration.⁵⁶

demonstrated with the help of spectroscopic evidence and density functional theory (DFT) calculations during the NO and SO₂ plasma-based removal and formation of intermediates by *in situ* SERS. Moreover, this study provided novel identification of such surface species with their vibrational modes, molecular adsorption, and orientation while adsorbed on Ag NPs through experimental as well as DFT studies. Similarly, different SERS substrates were designed to detect SO₂ and NO₂ in different kinds of samples.^{89,95–99}

Kumar *et al.* and Sharma *et al.*^{42,90} developed a SERS-based NH₃ sensor for the detection of NH₃ gas using a substrate composed of Au NPs decorated onto partial embedded 2D polystyrene colloidal crystals (PSCCs), partially

embedded into flexible polydimethylsiloxane (PDMS) elastomer. SERS signals of NH₃ molecules were found to be enhanced with an increase in NH₃ concentration from 100 to 1000 ppm. Zhang *et al.*¹⁰⁰ recently demonstrated that low concentration detection of NH₃ could be possible by *in situ* SERS detection. Rae *et al.*²³ investigated CO and N₂O gas sensing using AgPd SERS substrates, where the maximum enhancement factor that could be achieved was 10⁵. Sharma *et al.*⁴² designed an effective SERS substrate composed of Au NPs decorated on a controlled morphology of 2D PSCCs (200–500 nm diameter), partially embedded into flexible PDMS elastomer for SERS sensing of various gaseous molecules NH₃, H₂O₂, N₂O, and H₂S. Design of such nanostructure with Au NPs (of size 8 nm) deposited by radio



frequency (RF) magnetron sputtering on PSCCs creating a hot spot with large electromagnetic enhancement provides excellent SERS sensitivity and reliability. It occurred due to the self-assembled flexible hexagonally close-packed PSCCs producing 75 and 25 nm voids in the 500 and 200 nm PSCCs monolayers acting as an effective plasmonic propagator for SERS sensors signal.⁹⁰

3.2 SERS detection of VOCs and other gases

As discussed in section 1, several VOCs could be present in the environment and have been investigated using SERS

sensing applications. For example, Wong *et al.*¹⁰¹ proposed multiplex SERS-based detection of VOCs using leaning pillar substrates (*i.e.*, Si nanopillars coated with Ag). The Si nanopillars were 50–80 nm wide, and their heights were found to be 600–1600 nm. These specially designed leaning pillar substrates with Ag tips on the top exhibited better adsorption of the VOCs analyte molecules resulting in enhanced Raman signal attributed to the LSP ‘hot spots’ between adjacent leaning nanopillars. Using these Ag–Si SERS active substrate systems, a multiplex detection for mixed acetone and ethanol VOCs was investigated, and these VOCs in different ratios were successfully detected in a

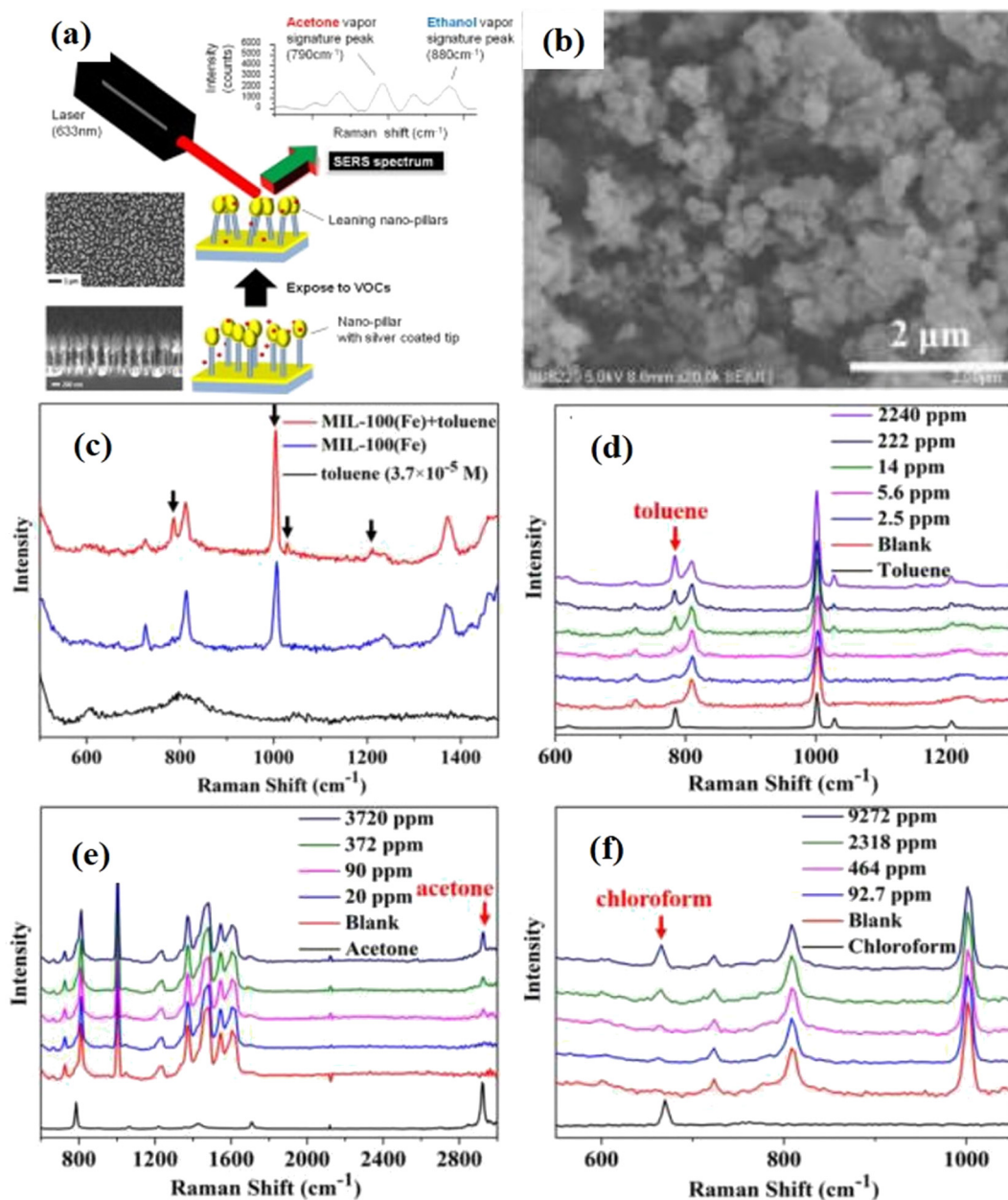


Fig. 4 (a) SEM micrographs of the nanopillar with a schematic of SERS detection. Reprinted with permission from ref. 101 (b) SEM micrograph of MIL-100(Fe) (c) SERS spectra of the toluene solution, its vapour and SERS substrate, and (d)–(f) are the SERS spectra of toluene, acetone, chloroform vapors, respectively, on SERS substrate. Reprinted with permission from ref. 72.



multiplex format. The limits of detection were found to be 0.0017 and 0.0037 ng for ethanol and acetone vapor molecules, respectively. These designed nanopillar substrates

exhibited a state-of-the-art Raman enhancement over large areas, as shown in Fig. 4(a). The novelty of leaned pillars with Ag tips was their large aspect ratio, which provided flexibility

Table 1 Various nanomaterial-based SERS substrates, their morphology and fabrication methods along with experimental results in SERS detection of various gases/VOCs

| S. No. | Nanostructures as SERS substrate/morphology | Method of fabrication | Detection of gases and VOCs | Important results/observation | Ref. |
|--------|---|---|--|--|--------|
| 1. | ZIF-8 wrapping on Au-dotted Ag-NWs | Solvothermal polyol method | CO ₂ | High selectivity for CO ₂ molecules with good stability and repeatability | 91 |
| 2. | Crystals SiO ₂ /TiO ₂ core/shell beads | Atomic layer deposition of TiO ₂ on SiO ₂ spheres | CO ₂ | Real time detection of CO ₂ as a function of different temperature | 88 |
| 3. | 3D Au coated 1D Ag NWs | Vacuum filtration of an Ag NW solution through a porous microfiber filter followed by Au sputtering | NO ₂ | On-site detection of LOD 0.1 ppm NO ₂ due to the high density of hot spots | 56 |
| 4. | 3D nanoporous architecture composed of Ag NWs deposited with Au hemispheres | Vacuum filtration of an Ag NW solution through a porous microfiber filter followed by Au sputtering and thermal annealing | NO ₂ | Extremely sensitive and rapid detection of NO ₂ gas to 10 ppb using a simple handheld Raman spectrometer | 93 |
| 5. | AgPd NPs | Simple colloidal chemistry method | CO and N ₂ O | SERS EF of 4×10^5 for CO and 1×10^5 for N ₂ O | 23 |
| 6. | Au NPs decorated 2D PSCCs partially embedded in the flexible PDMS substrate | Self assembled 2D PSCCs deposited with Au NPs by RF magnetron sputtering | NH ₃ , H ₂ O ₂ , N ₂ O, and H ₂ S | Sensing response, strongly dependent on the crystal size | 42, 90 |
| 7. | Si nano-pillars coated with Ag | Si nanopillars were fabricated by reactive ion etching process followed by Ag coating using electron beam evaporation | Acetone and ethanol | Higher LSPR response due to hot spots between adjacent leaning nanopillars leading to the LOD 0.0017 and 0.0037 ng for acetone and ethanol, respectively. EF $\sim 10^{11}$ | 101 |
| 8. | Au@ZIF-8 core-shell NPs | Citrate reduction method for Au NPs followed by controlling the ZIF-8 shell thickness through quenching terminated the reaction process | Toluene, ethylbenzene, and chlorobenzene | Owing to the excellent gas adsorption of the ZIF-8 shell and the LSPR effect of the Au core, Au@ZIF-8 NPs with a shell thickness of 3 nm exhibited better SERS enhancement | 103 |
| 10. | Ag NPs modified PVP | Chemical reduction method for Ag NPs | Ethanol | Act as a potential SERS substrate for VOCs | 102 |
| 11. | PDMS-coated Au@Ag NPs | Au@Ag NPs prepared by a seeds growth method followed by AgNO ₃ solution treatment and PDMS | Aromatic VOCs | Greater adsorption by PDMS and strong LSPR of plasmonic NPs resulted in about two orders of magnitude SERS enhancement as compared to only NPs | 104 |
| 12. | 3D Ag/Si membranes | Reduction of Ag on Si wafer followed by photoelectrochemical etching | Hydrazine | LOD of hydrazine was found to be 0.1 ppm from the vapor phase. EF of 10^4 was achieved | 2 |
| 13. | Au NPs and MIL-100 (Fe) MOFs | Au NP colloid solution was prepared and dropped on MIL-100(Fe) MOFs | VOCs such as toluene, acetone, chloroform, etc. | The LOD of MIL-100(Fe) for toluene was found to be 2.5 ppm, which was better with Ag-MOFs and decreased to 0.48 ppb due to "hot spots" in between Au NPs, resulting in EF of 10^{10} | 72 |
| 14. | 3D Ag/Si membranes | Reduction of Ag on Si wafer followed by photoelectrochemical etching using 3D printing | Anisole vapor | Synthesized SERS substrates achieved ppb sensitivity and identification in gas detection | 105 |
| 15. | Au NPs (variable sizes) | Salt reduction followed by UV-assisted photo-chemical reduction approach | Dinitrotoluene vapor | EF of 5.6×10^6 (for 117 nm Au-NPs) | 106 |
| 16. | Au NPs | Salt reduction followed by UV-assisted photo-chemical reduction approach | 4-Nitrophenol vapor | A detection limit of 0.5 ppb was achieved | 107 |
| 17. | PDMS coated Au NPs monolayer film | Seed growth method of Au NPs followed by PDMS coating | Toluene, nitrobenzene, benzene | LOD of 0.5 ppm, 0.6 ppm, and 78 ppm for toluene, nitrobenzene, and benzene, respectively | 108 |
| 18. | Ag film over a nanosphere (AgFON) | Ag films (200 nm thick) were deposited over silica nanosphere using the thermal vapor deposition system | Benzenethiol | LOD 6 ppm | 109 |
| 19. | Silver nanofilm (AgNF) with NPs of ~42 nm diameter | — | SO ₂ | Label-free assay, but with higher sensitivity with LOD of 10^{-6} M | 89 |
| 20. | Au NPs modified onto quartz fibres | Seeds growth method of Au NPs | Gas-phase VX and HD | (LOD) of $0.008 \mu\text{g L}^{-1}$ and $0.054 \mu\text{g L}^{-1}$ were achieved for VX and HD, respectively | 110 |



for leaning towards nearby pillars, creating self-assembled electromagnetic hot spots when illuminated by the laser. A SERS ultrasensitive device to detect ethanol vapor composed of Ag NPs of size 60 nm modified polyvinylpyrrolidone (PVP) was proposed by Wang *et al.*¹⁰² Chen *et al.*¹⁰³ demonstrated that Au@ZIF-8 core-shell nanostructures with 55 nm Au NPs and a shell thickness of 3 nm exhibited better SERS response for the detection of various VOC gas molecules, such as toluene, ethylbenzene, and chlorobenzene. Similarly, Xia *et al.* proposed PDMS-coated 1-propanethiol-modification of Au@Ag NPs for enhanced sensitivity of various aromatic vapors in the atmospheric environment.¹⁰⁴ 50 nm Au@Ag NPs were prepared by first synthesizing Au NPs of 30 nm through epitaxial growth, followed by treatment with AgNO₃ solution and PDMS. It was found that due to greater adsorption by PDMS and strong LSPR properties of Au@Ag NPs, there was SERS enhancement of about two orders of magnitude compared to only NPs.

Recently, Snitka *et al.*² developed a hybrid SERS platform of Si membrane and Ag NPs with a high density of 'hot spots' for molecular trace detection of various VOCs in the environment. First, 3D Ag/Si SERS substrates were prepared by using a Si wafer immersed in AgNO₃ and HF solution, followed by the formation of micro-pores through a photoelectrochemical etching process. The LOD of hydrazine was found to be 10⁻¹² mol L⁻¹ from the solution and 0.1 ppm from the vapor phase. Whereas 0.5 ppb LOD was recorded for anisole vapors in the air using Si-Ag hybrid SERS membrane platform. It was concluded that such hybrid systems could be designed for sensing in space applications. Similarly, Nemciauskas *et al.*¹⁰⁵ fabricated novel 3D printed SERS-based molecular sensors composed of nanoplasmonic Si membrane integrated with a gas micropump. The membrane-based sensing platform exhibited high sensitivity of 4.6 × 10⁻⁹ M towards anisole vapors. Fu *et al.*⁷² studied the role of MOFs as SERS substrates for the ultrasensitive multiplex detection of toluene and other VOCs. Au NPs and MIL-100 (Fe) MOFs system, as shown in Fig. 4(b), was used as an ideal SERS substrate, and a multiplex sensing of VOCs such as toluene, acetone, chloroform, *etc.* was demonstrated, as shown in Fig. 4(c-f). A high order EF was achieved for toluene, and it was also demonstrated that it could be useful for diagnostic lung cancer with a ppm detection limit in the human body. It was also demonstrated that the process of adsorption and desorption of gases could be studied using real-time SERS technology and applied to the specific identification of intermediates in catalytic reactions. Several VOCs such as benzenethiol, 2,4-dinitrotoluene, pyridine, 4-nitrophenol, toluene, benzene, nitrobenzene, and aromatic vapors have been detected using SERS as a probe for different purposes.^{104,106-109} Heleg-Shabtai *et al.*¹¹⁰ reported ultrasensitive detection of gas-phase VX and HD, which are toxic chemical warfare agents (CWA) and nerve agents (NAs).

The above gas sensing experiments and their fruitful results exhibit the applicability of Raman technology to the environment as well as homeland security. Some recent

reviews could be referred to for the detailed study of VOCs detection using SERS.^{111,112} The above discussion reveals that the synthesis of nanomaterials with better morphology and surface properties is an important aspect for enhanced SERS detection of gases/vapours. Some important findings in this regard are summarized in Table 1. The nanostructures with 'hot spot' creating higher electromagnetic enhancement along with higher adsorption capability are promising SERS substrates in the case of gaseous molecular detection.

4. Emerging application of SERS for breath diagnosis in human health

There is great progress in the past few years in ultrasensitive gas detection in various fields of medical and environmental monitoring using the SERS technique, which has provided excellent results with high selectivity, sensitivity, and multiplex gas detection capability. In this section, the use of the SERS technique in breath diagnosis for healthcare applications is discussed.

4.1 For multiplex potential gas biomarker in the human breath of patients

Several toxic gases and VOCs can be produced by different biochemical and physiological processes in various parts of the human body, which are exhaled in human breath, for example, NH₃, NO_x, H₂S, alcohols, aldehydes, acids, ketones, *etc.* In case of any abnormal metabolic state or abnormal biochemical/physiological processes within the body, the level of these gaseous components would not be normal in the exhaled air of human breath. Importantly, detection of abnormally high concentrations of these gases in exhaled breath could be promising for identifying various diseases because these gases are biomarkers of some diseases.

The vibrational fingerprints of molecular structures provide specific Raman peaks for different gaseous molecules. Wong *et al.*¹⁰¹ first demonstrated the multiplex SERS detection of VOCs, which was found to be very useful for the detection of multiplexity gas biomarkers in human breath analysis for the diagnosis of various diseases. Recently, Chen *et al.*²⁴ developed SERS based approach to detect VOCs biomarkers using Au NPs and reduced graphene oxide (GO) nanocomposites for both simulated and real breath samples with ultra sensitivity and multiplexing. These Au NPs-reduced GO SERS samples were fabricated by depositing Au NPs on the reduced GO, which provides excellent LSPR properties and adsorption properties for the VOC biomarkers to be adsorbed on the surface, resulting in the enhancement of SERS signals (Fig. 5I). As shown in Fig. 5II (A and B), the simulation provided well-defined clusters for the simulated breath of healthy persons (a), early gastric cancer (EGC) (b), and advanced gastric cancer (AGC) (c) patients. The relation between 14 Raman bands corresponding to the VOC biomarkers was studied and summarized. The 14 Raman bands in the Raman spectra



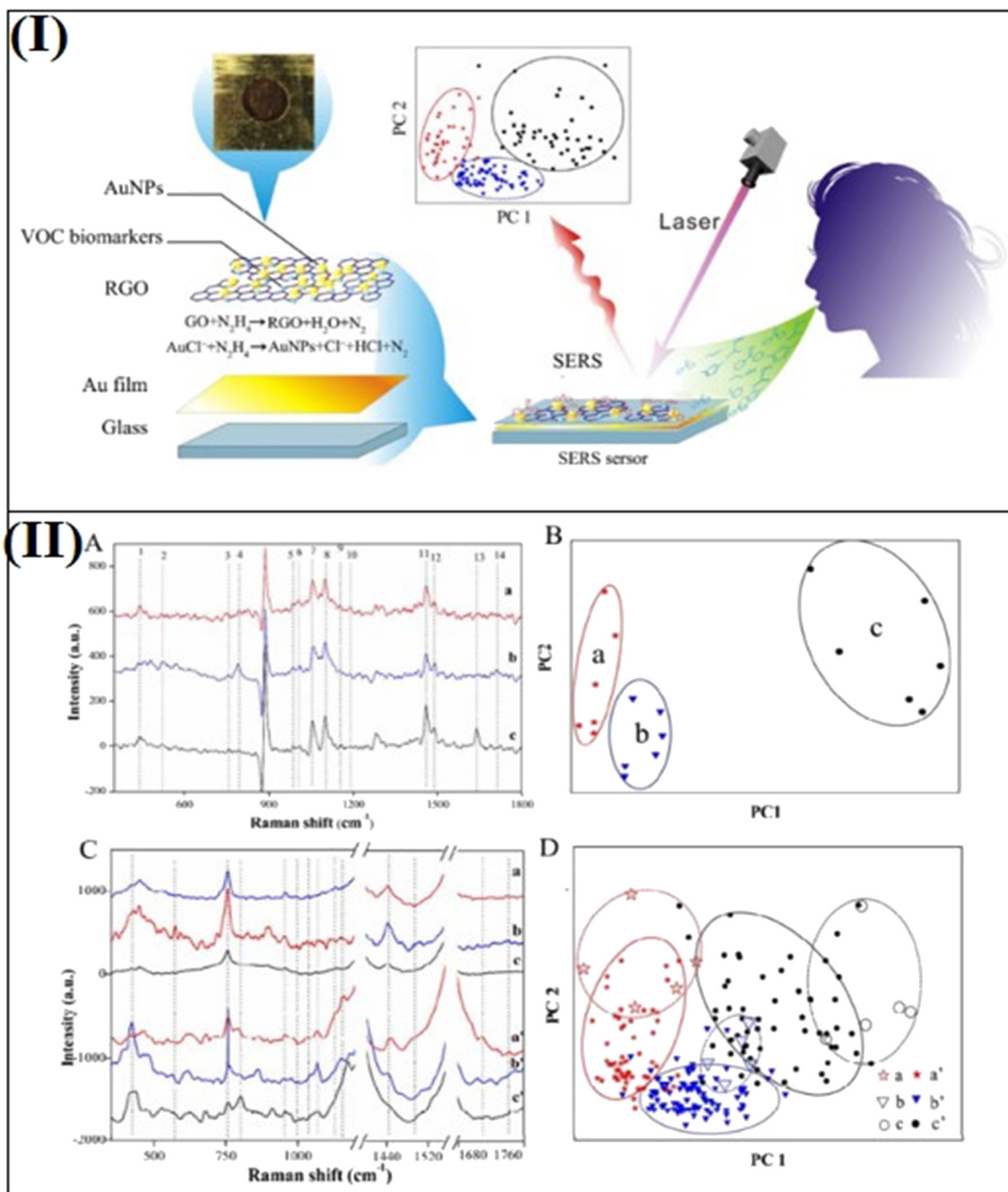


Fig. 5 (I) Schematic of SERS sensing tool and involved breath analysis. (II) (A) SERS spectra of VOC biomarker patterns. (B) PCA of the data set of biomarker patterns of healthy persons and EGC and AGC patients. Each data point in the PCA corresponds to the area of 14 bands in the processed SERS spectra. (C) SERS spectra of simulated and real breath samples of healthy persons and EGC and AGC patients. (D) PCA of the data set of simulated and real breath samples of healthy persons and EGC and AGC patients. Each data point in the PCA corresponds to the area of 14 bands in the SERS spectra. Reprinted with permission from ref. 24.

were taken as the fingerprints of biomarker patterns to distinguish EGC and AGC patients from healthy persons and were used for breath analysis based on the Au-GO SERS sensor. Fig. 5II (C and D) show the SERS spectra of simulated and real breath samples of healthy persons along with EGC and AGC patients. This experiment provides a way to distinguish EGC and AGC patients from healthy persons by monitoring the exhaled breath samples from the patients.

Similarly, Fu *et al.*⁷² demonstrated the detection of VOCs using the SERS technique, which could be helpful in the early diagnosis of lung cancer. The MIL-100(Fe) platform with Au NPs onto this was employed to detect toluene and other VOCs. The limit of detection for toluene gas as a biomarker for lung cancer was 0.48 ppb with an EF of 10^{10} . This is an emerging area in which the SERS technique could be potentially applied for the analysis of human breath to



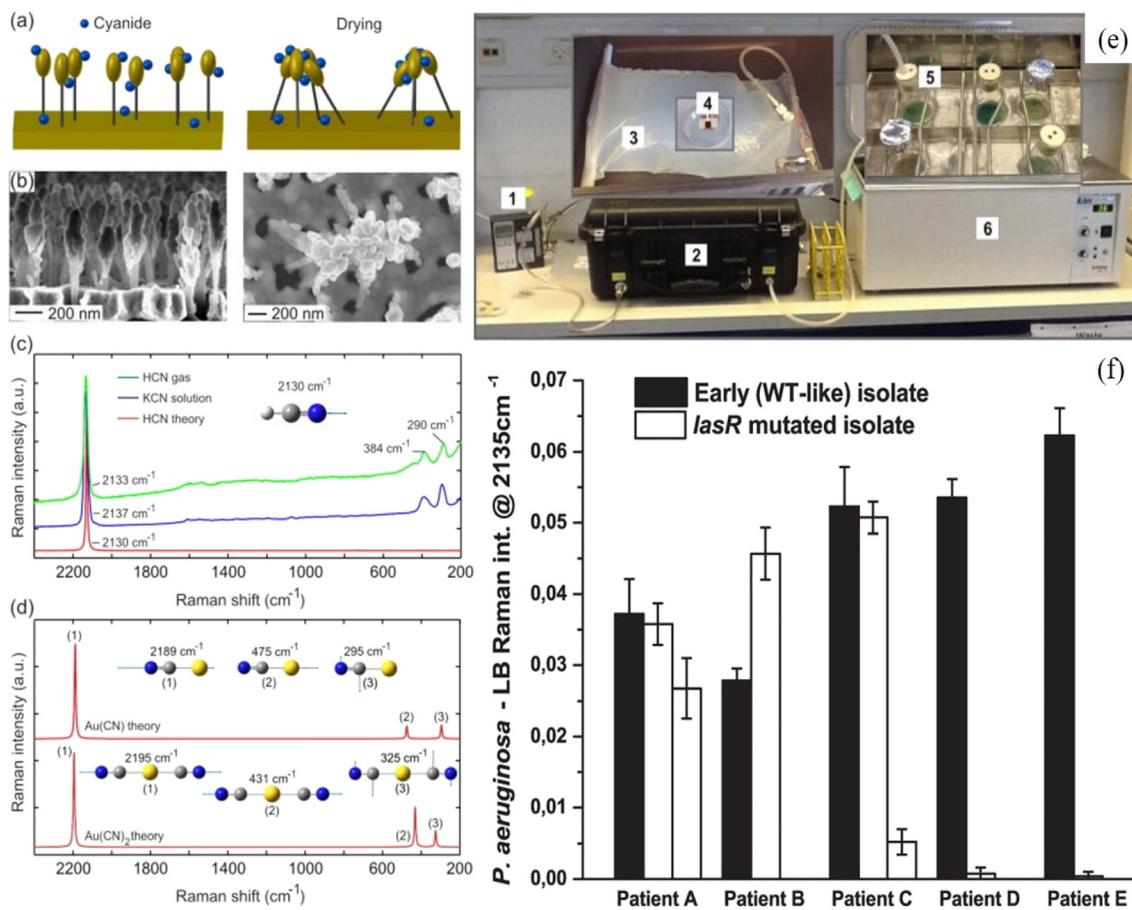


Fig. 6 Schematic of leaning of nanopillars (a) and SEM images (b) before and after leaning (courtesy of Kaiyu Wu). (c) SERS spectra of HCN(g) and KCN(aq) and theoretical Raman spectrum of HCN. (d) Theoretical Raman spectrum of Au(CN) and Au(CN)₂.¹¹⁴ (e) Demonstration of experimental set-up and detection of HCN using SERS substrate and (f) cyanide production of clinical *P. aeruginosa* overnight cultures from 5 CF patients. SERS detection of the biomarker hydrogen cyanide from *Pseudomonas aeruginosa* cultures isolated from cystic fibrosis patients.¹¹³

monitor human health. Lauridsen *et al.*^{113,114} developed SERS based breath nanosensor composed of Au-coated Si nanopillars and studied the SERS detection of hydrogen cyanide (HCN) at ppb level for human breath analysis (Fig. 6a and b). These Au-coated Si nano-pillar SERS substrates were fabricated by reactive ion etching of Si wafer followed by sputtered Au deposition. It formed 225 nm Au caps on Si nanopillars producing hot spots with an enhanced electromagnetic field for SERS detection. The detection of HCN is known to be a *Pseudomonas aeruginosa* (PA) biomarker for lung infections in cystic fibrosis (CF) patients. In HCN, a Raman band at ~ 2133 cm⁻¹ shows the characteristic peak due to the presence of a triple bond between C and N in cyanide. This is the novel characteristic of HCN detection using SERS.

A direct HCN SERS detection was performed first in the gas phase by exposing 5 ppm HCN on Au coated Si nanopillar substrate and correlated with the theoretical SERS spectrum of HCN on Au. Fig. 6(c) shows the SERS spectra in both gas (HCN) and liquid (KCN) with Raman band at 2133 cm⁻¹. Experimentally observed Raman bands at 290 and 384 cm⁻¹ were explained by theoretical calculations, which showed the

formation of Au–cyanide complexes (Fig. 6(d)). Fig. 6(e) shows the experimental setup of HCN detection using Au–Si nanopillar SERS substrates. Further, 12 clinical PA strains isolated from 5 CF patients and PA reference strains were studied for real practical application using SERS detection of HCN biomarker. As shown in Fig. 6(f), the intensity of the Raman band at 2135 cm⁻¹ exhibited by all early (WT-like) strains and also some of the *lasR* mutated strains isolated from pediatric CF patients corresponded to the C≡N stretching band. That indicated the emission of HCN from the CF patients, and it was concluded that PA infections could be detected at an earlier stage because daily breath sampling with an immediate output could be possible with a point-of-care SERS device.¹¹³ Similarly, Qiao *et al.*¹¹⁵ fabricated a ZIF-8 layer coated with self-assembled Au superparticles (GSPs) based SERS gas biomarker detector. The SERS substrate was designed to slow the flow rate of gaseous biomarkers and depress the exponential decay of the electromagnetic field around the GSP surfaces. The GSPs were functionalized by Schiff base reaction with 4-aminothiophenol for capturing the gaseous biomarkers. They studied the detection of gaseous aldehydes released as a



result of tumor-specific tissue composition and metabolism, thereby acting as indicators of lung cancer bombarding onto SERS-active GSPs substrates through a ZIF-8 channel. With the help of such an arrangement, gaseous aldehydes could be detected with a 10 ppb LOD. This experiment demonstrated the application of SERS for *in vitro* diagnosis of early-stage lung cancer. Interestingly, Park *et al.*¹¹⁶ demonstrated that SERS based substrates can also be used as a gas biomarker for living or dried plants through the detection of VOCs emitting from plants. Through SERS detection, it was possible to detect different VOCs and differentiate between healthy and caterpillar-infested plants.

As discussed above, biomarker detection using the SERS technique in human breath is a unique way to diagnose several diseases in the human body. Again, it is important to mention that designing SERS substrates through tailoring of shape or nano-architecturing is an important factor in enhancing the sensitivity for the gas biomarker at lower concentrations in the human breath. Porous nanomaterials embedded with plasmonic nanostructures could be better SERS substrates with higher adsorption capability of the gas species, resulting in higher sensitivity. In addition, 3D nano-architecturing with plasmonic hot spots with tunable gaps could be implemented for better results in the detection of gas biomarkers in human breath and diagnostics. Some important results have been summarized in Table 2, including nanostructured SERS substrates used for the detection of gas biomarkers in human breath indicating certain diseases in the human body.

4.2 Promising detection of SARS-CoV-2 in the breath of COVID-19 patients

Since 2020, the whole world has been fighting the most damaging coronavirus pandemic, and even after the development of many effective vaccines, provided little relax from the pandemic situation. There is still a chance of spreading more dangerous variants of the coronavirus. It shows the urgent need to develop novel technologies,

medical innovations, or innovative materials for controlling SARS-CoV-2 infection. The mode of infection of SARS-CoV-2 could be through the surface, air, or water.¹¹⁷ However, the problem of the coronavirus is still a question as 2nd and 3rd waves in 2021 and 2022, respectively, could not be controlled and more are expected in the future with a possibility of new corona variants. It has been reported in many surveys and recent articles that the spreading of coronavirus takes place *via* airborne transmission of the SARS-CoV-2 virus through aerosols.^{117,118} Efficient detection of SARS-CoV-2 from exhaled breath is required because it can provide a more accurate and direct way to detect the virus and minimize community transmissions.^{119,120} However, detection of SARS-CoV-2 in aerosols/breath and studying the risk of the same is not so easy and is challenging. Shan *et al.*¹²¹ demonstrated that a nanomaterial-based sensor array with multiplexed capabilities for the detection and monitoring of COVID-19 from exhaled breath could be possible. They fabricated a sensor composed of different Au NPs linked to organic ligands. The system developed a sensing layer that could be swelled or shrunk upon exposure to VOCs, leading to a change in the electric signals. Recently, Subali *et al.*¹²² presented a review on the potential of VOCs based breath analysis for COVID-19 screening using gas chromatography and mass spectrometry methods. It was concluded that COVID-19 patients showed a distinct pattern of VOCs in their breath analysis.

Li *et al.*¹¹⁸ fabricated a swirling aerosol collection device for collecting viral particles in exhaled breath emitted by a patient and subsequently detected SARS-CoV-2 using reverse transcription-polymerase chain reaction (RT-PCR). Recently, Viklund *et al.*¹²³ demonstrated that SARS-CoV-2 can be detected in exhaled aerosol/breath sampled during a few minutes of breathing or coughing. This is one of the most reliable diagnostic techniques for viral/bacterial infection along with some other techniques^{82,86} (Fig. 7). However, the RT-PCR method takes a long time to diagnose SARS-CoV-2 because of the required thermocycling steps.¹²⁴ Wu *et al.* recently demonstrated that SERS-based PCR detection

Table 2 Various nanostructured SERS substrates, their morphology, method of fabrication, and their applications in SERS detection of gas biomarkers in human breath for certain diseases

| S. No. | Nanostructures as SERS substrate/morphology | Method of fabrication | Gas biomarkers in human breath | Indication of related diseases | Ref. |
|--------|--|--|---|-----------------------------------|----------|
| 1. | Au NPs-reduced GO nanocomposites | GO prepared by Hummers method followed by deposition of a 300 nm thick Au film by sputtering | 14 VOC biomarkers in human breath | EGC and AGC | 24 |
| 2. | Au NPs and MIL-100 (Fe) MOFs | Au NPs colloid solution was prepared and dropped on MIL-100(Fe) MOFs | 4-Ethylbenzaldehyde, acetone, and isopropanol | Lung cancer | 72 |
| 3. | Au coated Si nanopillars | Reactive ion etching of Si wafer followed by Au sputtered deposition | HCN is known to be <i>Pseudomonas aeruginosa</i> (PA) biomarker | Lung infections in CF | 113, 114 |
| 4. | ZIF-8 layer coated with Au superparticles | Au superparticles synthesized by microemulsion assembly method coated by a ≈ 150 nm thick shell of ZIF-8 | Gaseous aldehydes | Early-stage lung cancer | 115 |
| 5. | Tenax-TA deposited on a layer of Ag-nanosphere | Ag nanosphere from AgNO ₃ reduction followed by a coating of Tenax-TA polymer solution | Cotton VOCs | Caterpillar infestation in plants | 116 |



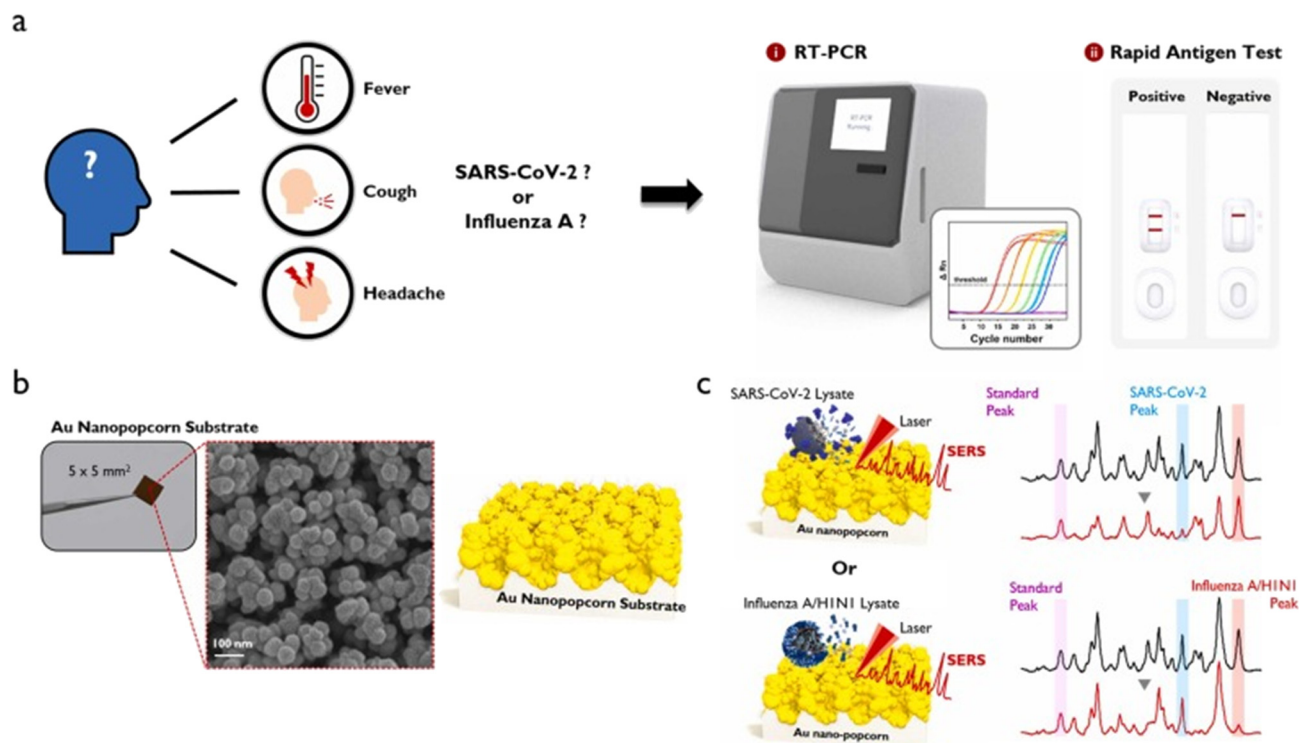


Fig. 7 (a) Symptoms that appear when infected with SARS-CoV-2 or influenza A, and RT-PCR and rapid antigen kit for their diagnosis. (b) Photograph and SEM image of Au nanopopcorn substrate. (c) Working principle of dual aptamer-immobilized Au nanopopcorn substrate for virus assays. Reprinted with permission from ref. 86.

method using Au NPs could be useful in shortening the diagnosis time.¹²⁴ SERS is a paradigmatic example of a nanomaterial-based highly sensitive diagnostic method as it has shown its potential with great capability for very low-level specific identification of various viruses, bacteria, and other pathogens.^{125,126} The use of SERS in the detection of viruses/bacteria is promising because of its feasibility in biosensing. As discussed above, it is a simple technique that utilizes SERS-active nanomaterials as substrate and a Raman spectrometer for the detection of biochemical structures and can be used in the fast detection of viruses like SARS-CoV-2 virus.^{125,126} It is better than a biochemical-based diagnosis, which needs many chemicals and other complicated processes.

Recently, Chen *et al.*⁸⁶ developed SERS-based dual functional sensor for rapid classification of SARS-CoV-2 and influenza A/H1N1 infection (Fig. 7). Au nanopopcorn based SERS substrate was fabricated and DNA aptamers that selectively bind to SARS-CoV-2 and influenza A/H1N1 were immobilized together on Au nanopopcorn substrate. Raman reporters (Cy3 and RRX), attached to the terminal of DNA aptamers, could generate strong SERS signals in the nanogap of the Au nanopopcorn substrate. When SARS-CoV-2 or influenza A virus approached the Au nanopopcorn substrate, the corresponding DNA aptamer selectively detached from the substrate due to the significant binding affinity between the corresponding DNA aptamer and the virus resulting in the SERS intensity change with increasing target virus

concentration. In this way, it was concluded that it could be possible to estimate whether a suspected patient is infected with SARS-CoV-2 or influenza A using the SERS-based DNA aptasensor as shown in Fig. 7.⁸⁶

There is limited use of SERS-based diagnosis of SARS-CoV-2 virus, which shows its great potential to be used for fast screening of SARS-CoV-2 virus and suitable for such pandemics.⁸⁷ In a recent review, Liu *et al.*⁸⁷ discussed an overview of fundamental knowledge about the SERS mechanism, including chemical and electromagnetic field enhancement mechanisms, the design and fabrication of SERS substrates based on materials, progress in using SERS for point-of-care testing in biochemical sensing, including SARS-CoV-2 virus and its clinical applications. SERS technique has been used to identify a Raman fingerprint of SARS-CoV-2 in the saliva of patients affected by COVID-19.^{85,128} As an immune response to COVID-19 infection, generally, patients produce SARS-CoV-2-specific antibodies, which are directed against specific proteins.^{82,127} SERS has been used for the detection of SARS-CoV-2-specific antibodies IgM/IgG in sera of COVID-19 patients using conventional lateral flow assay.^{129–131} Daoudi *et al.*¹²⁷ demonstrated SERS sensing of SARS-CoV-2 S1 spike protein of the SARS-CoV-2 virus family by fabricating AgNPs/SiNWs nanohybrid based sensors, as shown in Fig. 8(step 1–3). The Si NWs have an important impact on SERS, not only by increasing the specific surface area but also by enhancing the local electromagnetic field.^{132,133} Furthermore, the flexible SERS



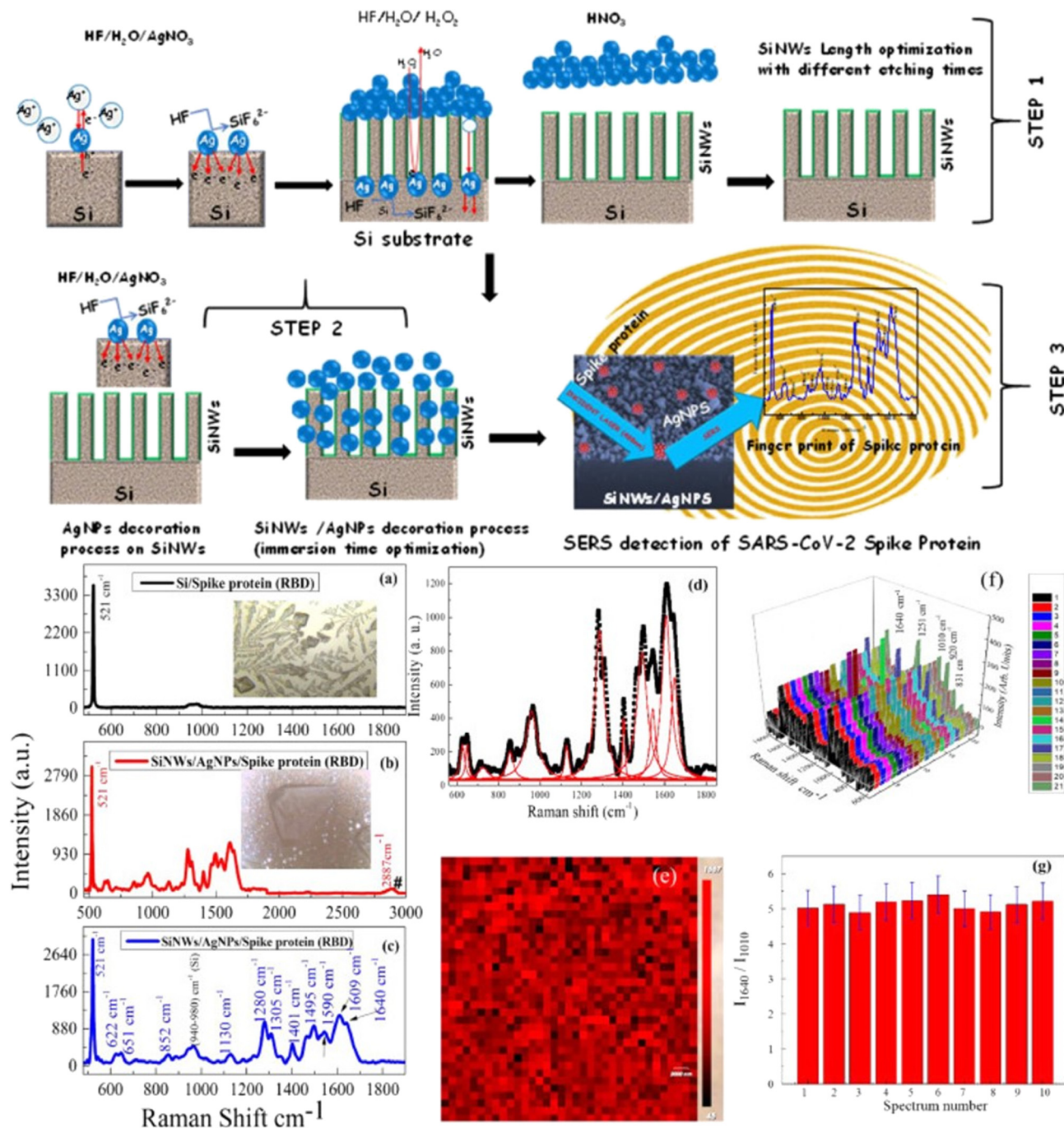


Fig. 8 Step 1-3: Schematic for fabrication and fast optical detection of the spike protein of the SARS-CoV-2 using Si-Ag based SERS substrates. Raman spectra of SARS-CoV-2 spike protein on (a) flat Si and Si-Ag based SERS substrate between (b) 500 cm⁻¹ to 3000 cm⁻¹ and (c) 500 cm⁻¹ to 1800 cm⁻¹. Insets are the optical microscopy images of spike proteins. (d) Lorentz fit for the experimental data (e) mapping of spike protein detection on SERS substrate. (f) Various scans taken randomly at many points and (g) the corresponding statistical analysis of Raman peak intensity ratios (I_{1640}/I_{1010}) for 10 different positions. Reprinted with permission from ref. 127.

substrates are more conducive to gas detection.¹³⁴ These were prepared by reactive ion etching and Ag NPs deposition. These SiNWs/AgNPs SERS-based sensors were used to detect the spike protein at a concentration down to 9.3×10^{-12} M. Strong and dominant Raman peaks at 1280, 1404, 1495, 1541, and 1609 cm⁻¹ were observed at a fraction of a minute corresponding to various CH₂ wagging

more of several amino acids of spike proteins present in the virus (Fig. 8a-g).¹²⁷

Zhang *et al.*¹³⁵ demonstrated that using portable Raman spectrometers and Ag-nanorod (of diameter and length of 211 ± 45 and 737 ± 52 nm, respectively)-based SERS substrates, ultra-fast and onsite interrogation of SARS-CoV-2 in water could be carried out within 5 min. These Ag nanorod



based SERS substrates were prepared by oblique angle deposition on Si substrate by electron evaporation/sputtering method. More than 23 water samples were tested with accuracy onsite, which proved that it has the potential to be used as an easy and portable measurement for spot detection of SARS-CoV-2 to evaluate disinfection performance and explore viral survival in environmental media. Similarly, Leong *et al.*¹²⁰ designed a noninvasive and point-of-care handheld portable SERS sensor-based breathalyzer containing a chip with Ag nanocubes (of length 120 ± 5 nm) as SERS active substrates. It was explained that the exhaled breath could be filled into the breathalyzer of the SERS device for a few seconds, where the breath components would interact with the SERS active substrates. Once the breathalyzer was loaded into a portable Raman spectrometer, potential COVID-19 breath biomarkers could be detected by analyzing the SERS spectra. Breath VOC biomarkers have been detected for COVID-19,^{120,136} such as the work demonstrated by Leong *et al.*,¹²⁰ that SERS spectra of the breath of COVID-positive and -negative people were different in regions responsive to ketones, alcohols, and aldehydes. The collected data were used to develop a statistical model for COVID diagnosis, in which over 500 people were tested using the developed breathalyzer and compared with their RT-PCR tests. Results were found to be very close in both the tests; however, the SERS-based test could be performed very fast as compared to RT-PCR and was carried out on-site. It was concluded that developing this type of breathalyzer could be a potential tool to detect COVID-19 or any other viruses directly and would open a way to stop the community transmissions.

It is evident from the above discussed literature that SERS based detection of SARS-CoV-2 in the breath of COVID-19 patients is promising as compared to the traditional methods and the advancement of portable Raman spectrophotometer has made it more convenient. It provides a facility to do the detection on site without visiting the laboratory, which is generally not advised for COVID-19 patients. More efforts are needed to design and tailor the nanomaterials for tuning surface area and flexibility. It will help in tuning their SERS activity for better sensitivity to SARS-CoV-2 or other dangerous viruses.

5. Summary, challenges, and future prospects

The ultrasensitive detection of toxic and harmful gases is required for industrial process monitoring and environmental control as well as for medical diagnostics in human health. Nanomaterials are at the heart of nanotechnology and are being utilized as promising and primary materials for modern techniques in the field of energy, environment, and biomedical. In this context, nanomaterials based on the SERS technique is one of such techniques being used as a multidisciplinary tool in almost all field of science. This technique uses novel functional

nanomaterials based on noble metals or semiconductors, providing higher sensitivity and selectivity for the detection and sensing of chemical or biological molecules. SERS provides a rapid, highly sensitive/selective tool and direct evidence of analyte molecules as compared to the traditional gas sensing techniques with a special property of discriminating several molecules based on their unique vibrational fingerprints with a high spectral resolution.

In this review, the emerging application of SERS as a gas sensing tool for the detection of toxic and harmful gases has been discussed. Particularly, the use of SERS has been explored because of its emerging and potential applications for gas sensing in the environment and human health, with emphasis on the recent advances in these fields. In recent years, SERS has shown promising application in the detection of gas biomarkers in the human breath to detect related diseases in the human body, which has been discussed in detail. It is simpler and more favorable for sensing environmental gases or diagnostic human health using handheld portable Raman spectrometers. The detection of breath gases/VOCs using such a tool provides an excellent way to detect SARS-CoV-2 or similar viruses directly from the breath of the patient, which is at present limited by bulky instrumentation and inflexible analysis protocol. Recent advancements in detecting SARS-CoV-2 in the breath of COVID-19 patients have been discussed with emphasis on the use of portable SERS for direct and fast detection. There are only a few reports available on this important research in the literature.

However, the use of SERS nanotechnology has not been explored much yet in the field of environmental gas sensing or for the detection of gas biomarker/SARS-CoV-2/other viruses in human breath and need more attention for practical applications in society. Therefore, there is a big scope for developing nanomaterial based SERS techniques in the field of environment and human health. This has led to several open platforms to work further and explore the research in several directions – (i) poor affinity of gaseous molecules on the surface of the metal NPs is a big challenge for ultrasensitive detection using SERS.² This interaction needs more experimental and theoretical work to provide a better protocol for surface modification or to develop efficient nanomaterials to better enrich molecules on the metallic surfaces for highly selective SERS gas sensors.^{91,93} (ii) In the case of environmental gas sensing, sometimes cooling of the substrate for better adsorption of the gas molecules on the surface of the SERS active substrate is required, which limits the practical applications and also stability of SERS measurement that need to be explored in the future research.¹⁰¹ (iii) Portable SERS technology could emerge as a promising candidate for point-of-care testing using SERS detection technology, which needs attention to explore.⁸⁷ (iv) For practical applications of the SERS technique, proper integration of SERS active nanomaterials with handheld portable Raman spectrometers is required for higher sensitivity and gas/virus selectivity capabilities.¹¹⁰ (v)



There is an urgent need to explore SERS based research for virus detection, such as SARS-CoV-2, for direct and fast detection, which is limited by the traditional approaches.⁸⁴ (vi) Looking at the current COVID-19 pandemic, the development of a highly sensitive, portable, and cost effective technique for direct breath analysis of COVID-19 patients or any viral infection would be a game-changer in this field of sensors and diagnostics.¹³⁷

In summary, the nanomaterial-based SERS technique is a promising sensing tool for various applications in the field of environmental control to human health for diagnosis. It has the potential to compete with other traditional methods with high sensitivity and selectivity. Eventually, it can play a vital role in the direct detection of SARS-CoV-2 in the exhaled breath of COVID-19 patients with portable applicability for fast detection, which is the need of the hour and has a lot of future research possibilities to work in this direction.

Conflicts of interest

The authors declare that they don't have any known competing financial interests or personal relationships that could have appeared to influence the work reported in this review article.

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