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Sensing and Identification of Health Hazardous Molecular Components using Surface-Enhanced Raman Spectroscopy: A Mini Review

Pratiksha P. Mandrekar[1], Moonjin Lee[2], Tae-Sung Kim[2], and Daejong Yang[1,3,+]

Abstract

The use of various adulterants and harmful chemicals is rapidly increasing in various sectors such as agriculture, food, and pharmaceuticals, and they are also present in our surroundings in the form of pollutants. The regular and repeated intake of harmful chemicals often adversely affects human health. The prolonged exposure of living beings to such adverse components can lead to severe health complications. To avoid the unlimited utilization of these chemical components, a sensing technology that is sensitive and reliable for low-concentration detection is beneficial. Surface-enhanced Raman spectroscopy (SERS) is a powerful method for identifying low-range concentrations of analytes, leading to great applications in molecular identification, including various diagnostic biomarkers. SERS in chemical, gas, and biological sensors can be an excellent approach in the sensing world to achieve rapid and multiple-analyte detection, leading to a new and efficient approach in healthcare monitoring.

Keywords: Surface-enhanced raman spectroscopy (SERS), Chemical sensor, Gas sensor, Biomolecular sensor, Health hazardous molecular component

1. INTRODUCTION

In today's fast-paced world, technological and lifestyle developments are observed and experienced daily. Undoubtedly, modern inventions have made life comfortable. However, a significant portion of this progress has resulted in the use of various gases and chemicals that cause numerous health-related complications [1]. Various chemical pesticides [2,3], insecticides [4,5], preservatives [6,7], and dyes [8,9] are widely used to keep eatables fresh, appealing, and for pest attack prevention. Long-term consumption of these products can lead to various health complications, some of which can be severe [10-12]. Besides the food-related overuse of chemicals, other factors also affect human health, such as gases released from landfills and sewage, often referred to as volatile organic compounds (VOCs) [13] and greenhouse gases [14].

Considering the health risks related to the consumption and exposure to these injurious elements, it is necessary to determine whether they are used unnecessarily or over the prescribed limit. The major requirements of the sensing mechanism are proper, hustle free and sensitive molecular identification of various chemicals and gas molecules. SERS is an emerging analytical technique that proves useful for trace-level molecular detection and identification [15]. Raman spectroscopy provides label-free characterization of molecules or analytes, where each molecule exhibits a specific Raman band position and intensity, which are called the fingerprints of the molecule [16]. Therefore, it is possible to identify more than one analyte in a mixture of samples using Raman spectroscopy. However, the Raman scattering spectral intensities are very low, limiting their application to pure or concentrated samples [17]. To overcome this drawback, SERS is a compelling method for enhancing the signal intensity of normal Raman spectra. This is due to the occurrence of surface plasmon resonance, which causes an oscillating electric field of incident light on the metal nanostructures or nanoparticles (NPs) used [18]. The hotspots in the assembly of nanomaterials play an important role in signal amplification [19-21]. Apart from chemical sensing, SERS can also be utilized for biomedical sensing, where identification is possible by analyzing various disease-related biomarkers and their increased production in the body. Disease biomarkers include ions, toxins, microbes, and

[1]Department of Future Convergence Engineering, Kongju National University, Cheonan, 31080, Republic of Korea
[2]Ocean and Maritime Digital Technology Research Division, Korea Research Institute of Ships and Ocean Engineering, Daejeon, 34103, Republic of Korea.
[3]Department of Mechanical and Automotive Engineering, Kongju National University, Cheonan, 31080, Republic of Korea
[+]Corresponding author: daejong@kongju.ac.kr
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living cells [22,23].

In this review, we highlight the various potential applications of SERS substrates in terms of chemical sensing of food items used in our day-to-day life, gas sensing, and biomolecular detection of various diseases, which can be very advantageous in the medical field for easy and early identification. The aim was to emphasize the possibility of using SERS and SERS sensing abilities as convenient, reliable, and sensitive technologies to improve human health and well-being.

2. SERS SENSING APPLICATIONS

2.1 Chemical Sensing

Food additives and pesticides are widely used in the agricultural sector and are packed or ready-to-serve food items. The primary purposes of such adulterants are protection, preservation, texture improvement, and enhancing appearance. However, this often results in the excessive use of these chemical components, leading to various adverse effects on human health with prolonged consumption.

Therefore, it is essential to measure the contents of these materials, and SERS can be employed for this purpose. In particular, packaged and edible drinks are often laced with such products to increase their shelf life. Numerous studies have been conducted to simulate real samples by adding contaminants to food products and using SERS substrates for analysis. Thiabendazole (TBZ) food preservatives are frequently used in juices and drinks, and high doses or prolonged consumption can lead to thyroid hormone imbalances and liver damage. Xuan *et al.* [24] showed that the metal-organic frameworks (MOF) composed of terephthalic acid (PTA) and Fe^{3+} with gold and silver on the surface of MOF can be used to identify thiabendazole concentrations as low as 50 ppb in juice. Where the experimental procedure of this work showcased SERS spectra results indicating TBZ identification in the juice sample containing the TBZ contamination. The silver (Ag) NPs and MOF of Material of Institute Lavoisier 101 with Iron (MIL-101(Fe)) can be used for determining sodium thiocyanate (NaSCN) preservative in water and milk as low as 18.5 μg/L and 96.3 μg/L respectively. NaSCN long term intake could be resulting in low absorption of iodine in human body, and abnormal thyroid hormone disorder as suggested by Wang *et al.* [25].

Several other MOFs containing silver (Ag) and gold (Au) NPs have been utilized for pesticide detection. Among the common

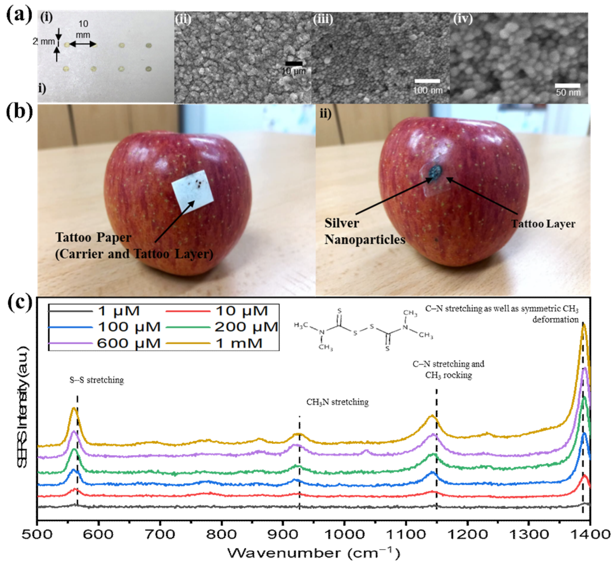

Fig. 1. (a)(i) Image of the flexible tattoo-paper SERS substrate with printed AgNPs, (a)(ii,iii,iv) SEM images of the silver AgNPs; (b) Sample collection on the apple surface contaminated with thiram; (c) SERS intensity spectra of the apple specimens showing peak intensities at 560 cm^{-1}, 933 cm^{-1}, 1144 cm^{-1} and 1382 cm^{-1} for the different concentration of ranging from 1 μM to 1 mM of thiram solutions. Reprinted with permission from Ref. [29]. Copyright (2023) MDPI.

pesticides and insecticides are parathion-methyl (PTM) and methenamine. Research conducted on the MOF of Au/Cys-Fe_3O_4/MIL-101 by Zhu *et al.* [26] successfully detected PTM at 5 ppb in juice, and that on the MOF of Au@MIL-101(Fe) by Cai *et al.* [27] effectively determined 1.0×10^{-9} M methenamine in vermicelli. New Coccine (NC) and Orange II (OII) in contaminated soft drinks and paprika were studied and identified with a low limit of detection (LOD) of 0.4015 mg/L for NC and 0.0546 mg/L for OII. The MOF used here was UiO-66(NH_2)@Au as reported by Wu *et al.* [28].

Besides MOF, SERS substrates containing AgNPs were also employed by Mandrekar *et al.* for thiram pesticide analysis on the fruit's surface, detecting concentrations as low as 1 μM [29], from the apple surface contaminated from concentration ranging 1 μM of lowest up to 1 mM of thiram. as illustrated in Fig. 1. This study involved fabricating a flexible tattoo-paper-based AgNPs substrate capable of identifying pesticides on curved surfaces of fruits and vegetables. Fig. 1(a) displays a photograph of the fabricated tattoo-paper-based SERS substrate with AgNPs, along with scanning electron microscopy (SEM) images. Fig. 1(b) showcases a sample collected from the fruit's surface using the tattoo-paper SERS substrate. Raman spectra of various concentrations of thiram solution on the fruit specimen's surface are presented in

Fig. 1(c). Similar chemical measurement of explosive molecules of trinitrotoluene (TNT) down to 10^{-10} M was carried out by Kong *et al.* [30]. The preparation of the AgNPs SERS substrates was carried out by in-situ growth method from electroless deposited seeds within the photonic nano porous diatom for the 3-dimentional (3-D) hybrid plasmonic–photonic were fabricated on crystal biosilica. Such SERS substrates showing impressive chemical identification qualities are very useful in terms of future applications for sensors based on chemical molecules.

2.2 Gas Sensing

The emissions of harmful and toxic gases into the atmosphere have increased in recent years. The major reasons for this could be increasing industrialization and vehicle transportation. Toxic gas emissions from such sources and occupational exposure can lead to poor health quality [31]. Hence, sensitive sensing techniques are of great importance to prevent and detect accidental leakage of such gases. SERS, with its excellent molecular identification qualities, can be utilized for such purposes. Ethanol and acetone vapors, classified as VOCs, are extensively used in industries and household applications, and they can be found in the air, posing harm to human health through long-term inhalation. Exposure to these VOCs can cause several health concerns, including headaches, drowsiness, eye irritation, and breathing difficulties [32,33]. Additionally, VOCs like acetone can serve as essential biomarkers for diabetes when detected in a patient's exhaled breath [34]. Multiplex SERS-based detection of VOCs, including acetone and ethanol vapors, has been achieved using SERS substrates of silicon nanopillars coated with Au carried out by Wong *et al.* [35]. The work exhibited detection of mixture of acetone and ethanol vapors with a low detection range of concentrations of 0.0017 ng and 0.0037 ng respectively. The results also proved to be great example to show the use of SERS sensing technique for multiple molecular analyses simultaneously.

There are various possibilities for the generation of other explosive and flammable gases and vapors in the air due to different reasons. SERS allows for the sensitive detection of such gaseous components. Among the numerous studies, one involved the detection of the explosive molecule 4-aminothiophenol (4-ATP) down to 10^{-8} M, utilizing gold nanowires (AuNWs) on two-dimensional graphitic carbon nitride nanosheets ($g-C_3N_4$/AuNWs) with reusability up to six cycles by Xu *et al.* [36]. Warfare agents, known for their explosive and destructive nature, can be highly dangerous. Study carried out by Lafuente *et al.* [37] identified dimethyl methyl phosphonate (DMMP) with a detection limit as low as 130 ppb in the gas phase using citrate-capped AuNP monolayers. Additionally, 2,4-dinitrotoluene (DNT) vapor was deposited on a polyethylene terephthalate (PET) sheet using a flexible AgNP ink SERS substrate and analyzed by Emamian *et al.* [38] successfully using Raman spectroscopy.

SERS substrates also have advantages in gas sensing for the food sector, where identifying spoiled eatables is crucial to ensure food safety. Spoiled food often releases specific odors and gases [39]. Chen *et al.* [40] suggested gold nano-bipyramids (Au NBPs) encapsulated by zeolitic imidazolate framework-8 (ZIF-8) (Au NBPs@ZIF-8) were successful in identifying 0.2 nM to 20 mM hydrogen sulfide (H_2S) gas released from spoiled fish meat. Sample collection and analysis process was carried out by storage of different fish samples of *C. saira, H. olidus,* and *L. polyactis* at different storage time durations of 0 h, 12 h, 24 h and 48 h such that the fish samples spoiled and the released H_2S gas which was then measured using handheld Raman spectrometer. The fabricated SERS had detection range of 0.2 nM to 20 mM with a LOD of 0.17 nM.

Work involving another zeolite framework, Au@ zeolite imidazolate-8 (ZIF-8) SERS, was able to recognize important volatile indicators for evaluating food spoilage, namely putrescine and cadaverine, with the lowest concentrations of 79.99 ppb and 115.88 ppb, respectively, in spoiled salmon, chicken, beef, and pork samples by Kim *et al.* [41]. The work done by Chen *et al.* [42] employed poly acrylic acid (PAA), poly methyl methacrylate (PMMA) and polydimethylsiloxane (PDMS) multiple SERS gas sensor matrix fabrication along with AgNP. Three target gases involved were phenethyl alcohol, acetophenone and anethole. Fig. 2(a) highlights the gas detection process in schematical form. Fig. 2(b)(i,ii,iii) are the resultant Raman spectra of phenethyl alcohol, acetophenone and anethole gases respectively. These studies shed light on the capabilities of SERS technology in gas sensing, demanding highly sensitive sensors with low-concentration range applications, making SERS a preferable option in gas-sensing applications.

2.3 Biomolecular Sensing

The human body tends to produce various abnormal biomolecular signals, which can be advantageous for identifying the early stages of various diseases or other health abnormalities in an individual [43-45]. These biomolecules can serve as key identification markers in SERS technology, and liquid biopsy, which involves analyzing biological liquid samples, can aid in

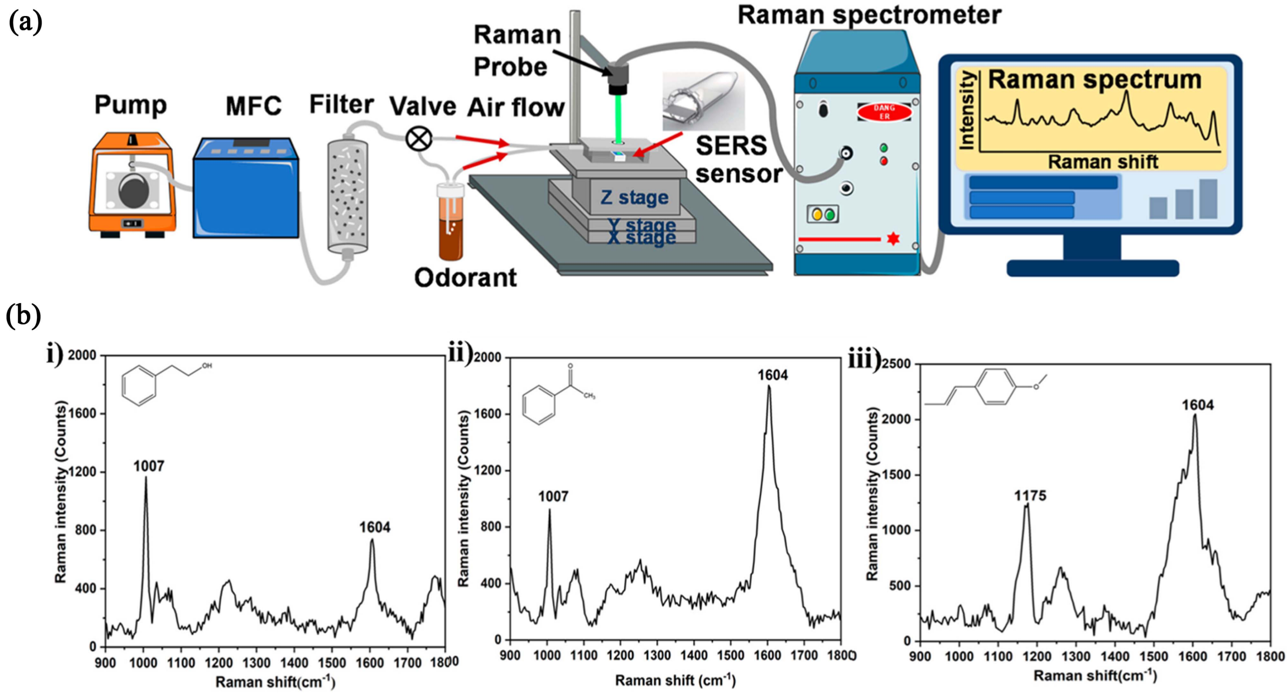

Fig. 2. (a) Schematic representation of gas generation and detection process; (b) Raman spectra of (i) phenethyl alcohol gas, (ii) acetophenone gas, (iii) anethole gas. Reprinted with permission from Ref. [42]. Copyright (2021) MDPI.

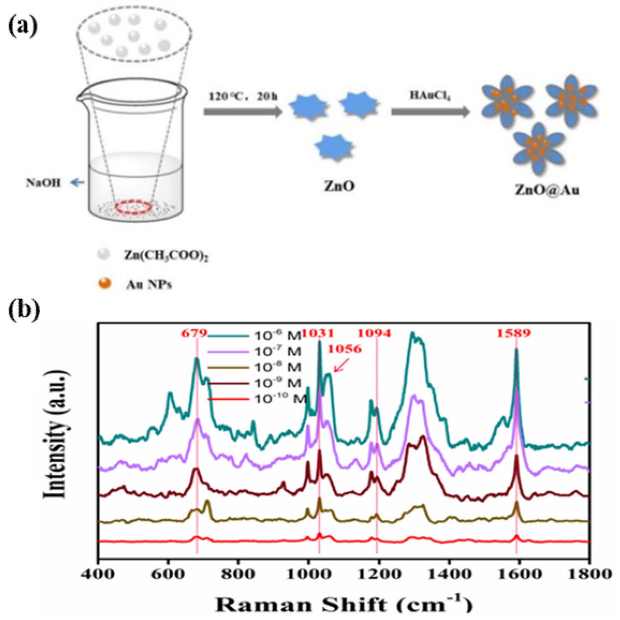

Fig. 3. (a) Schematic representation of hydrothermal fabrication of SERS substrates containing ZnO tips decorated with AuNP; (b) Raman spectra of different concentrations of nicotine in saliva. Reprinted with permission from Ref. [46]. Copyright (2021) MDPI.

biomarker recognition. Cao *et al.* [46] suggested that SERS substrate of zinc oxide (ZnO) tips decorated with AuNP can be advantageous for trace identification of nicotine in human saliva as low as 1×10^{-10} mol/L. The visual schematic representation of hydrothermal synthesis of the substrate is shown in Fig. 3(a). Raman spectra of various concentrations of nicotine in saliva samples is exhibited in Fig. 3(b). Peak at 1589 cm^{-1} was chosen for the nicotine detection due to easy observation without any spectral interference.

A peroxidase-mimicking nanozyme was developed by decorating magnetic ring-like iron oxide (Fe_3O_4) with AuNPs (R–Fe_3O_4/Au) by Huang *et al.* [47] for colorimetric and SERS dual-mode detection of biomolecules in human serum. This nanozyme facilitates detecting spiked biomolecules such as glutathione (GSH) and cholesterol in human blood serum. The substrate allows for the lowest sensing of glutathione (GSH) up to 0.10 µM and cholesterol up to a concentration of 0.08 µM, with substrate stability and reusability of up to 5 times.

Regarding the forensic use of SERS substrates, the work done by Atta *et al.* [48] using synthesized bimetallic gold nanostars covered with AgNPs (BGNS-Ag) SERS platforms provided excellent sensing capacity of cocaine and heroin in spiked water and human urine samples having the detection LOD as low as 10 pg/mL for cocaine and 100 pg/mL for heroin.

The SERS technique with an annealed AgNP/porous silicon Bragg mirror composite substrate was used for biomolecular analysis of breast cancer patient serum and comparison with healthy human serum samples as reported by Cheng *et al.* [49]. These results revealed that valine and collagen could be used as diagnostic biomarkers. Additionally, differences in the peak intensities of proteins, bases, carotenoids, and lipids are useful for comparison between normal and cancerous serum samples. The enhancement of such molecular intensities in cancerous samples compared to normal samples can be an indicator, considering the abnormal secretion in contrast to healthy individuals' samples.

Apart from liquid biopsy, SERS can be used for molecular reporter identification in cancer detection in cancerous and tumor tissues. Several studies have been conducted to detect breast cancer tissues and their biomarkers. Choi *et al.* [50] highlighted from his work of study use of polyethylene glycol (PEGylated) Ag-Au hollow nanospheres functional SERS tags in breast cancer cells Sk-Br3 and MDA-MB-231. The cell lines were analyzed for three cancer biomarkers: anti-epithelial cell adhesion molecule (EpCAM), anti-erythroblastic oncogene B2 (ErbB2), and anti-cluster of differentiation (CD44), involving Raman reporters for each biomarker, namely malachite green (MGITC), rhodamine B isothiocyanate (RBITC), and 3,3'-diethyithiatri carbocyanine iodide (DTDC), respectively. This study involved Raman mapping identification of cell lines. Also, Qiu *et al.* [51] carried out study involving Au@Ag core–shell nanoparticles, decorated with a double layer of Raman reporter on the surface of the Au core and Ag shell, functionalized with polyethylene glycol (HS-PEG-NHS), were fabricated for mapping tumor cell markers, specifically epidermal growth factor receptors (EGFR and ErbB2), and insulin-like growth factor 1 (IGF1). The Raman reporters used were similar to those reported in a previous study. Malachite green isothiocyanate (MGITC) for EGFR, rhodamine B 5-isothiocyanate (RBITC) for ErbB2, and 3,3′-diethyithiatri carbocyanine iodide (DTDC) for IGF1. Human normal mammary epithelial cell line (MCF-10A) and human breast cancer cell lines (KPL-4, SK-BR-3, and MDA-MB-468) were used for work. Therapeutic efficacy after chemotherapy and surgical treatment was also evaluated through SERS imaging in live mouse specimens where different organs of the mice were studied using Raman mapping for evaluating the effect of antitumor drug therapy and surgery treatment. Similarly, the breast cancer cell lines MDA-MB-231 and MCF-7 were subjected to SERS sensing of urokinase plasminogen activation receptor (uPAR) and EGFR as target peptides using GNS with Raman-active molecules 4-nitrothiophenol (NTP) and Diamino-1,3,5-triazine-2-thiol (DATT) by Li *et al.* [52].

3. CONCLUSION

This review focuses on the recent advances made in SERS technology, especially in terms of its sensing applications. The identification of numerous gaseous and chemical molecules is crucial for ensuring the health and safety of living organisms. SERS is a vibrational spectroscopy technique that is beneficial for highly sensitive structural detection of low concentration analytes and signal amplification due localized surface plasmons plays an important role in in the identification of the of minute concentrations. Although the experimental work and setups requires careful handling of sample and optical setup to ensure maximum signal generation and enhancement, it is a non-destructive technique for determining chemical identity and structural information from small numbers of molecules. SERS nanomaterial-infused substrates can serve as highly beneficial sensing devices, utilizing label-free Raman spectroscopy. The low-concentration sensitivity and possession of unique fingerprint spectra for each individual molecule make SERS a valuable tool for simultaneous identification of multiple analytes. It enables easy detection and identification of chemicals, gases, and biomolecules. Moreover, SERS can identify minute concentrations of target elements. Considering all the advantages and related study outcomes, it is safe to say that SERS can find wide-ranging applications in various fields for the future applications such as sensing and identifying the injurious adulterant may it be in consumable products, cosmetics, or drinks, as well as for the identification of various drugs and chemicals which are important in terms of regular safety checks and measures. Also, the employment of the SERS based sensors for harmful gases and vapors detection in the industrial facilities where the chances of gas leakage are likely to be happening or in the household facilities can be a great application in the future. In terms of future medical application of the SERS, it can be used in flexible skin attachment devices for the recognition of various biomarkers which can be helpful for the early disease identification.

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