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ORIGINAL ARTICLE

A review of applications of surface-enhanced raman spectroscopy laser for detection of biomaterials and a quick glance into its advances for COVID-19 investigations

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Abstract
Surface-enhanced Raman spectroscopy (SERS) is one of the most sensitive analytical tools. In some cases, it is possible to record a high-quality SERS spectrum in which even a single molecule is involved. Therefore, SERS is considered a significantly promising option as an alternative to routine analytical techniques used in food, environmental, biochemical, and medical analyzes. In this review, the definitive applications of SERS developed to identify biochemically important species (especially medical and biological) from the simplest to the most complex are briefly discussed. Moreover, the potential capability of SERS for being used as an alternative to routine methods in diagnostic and clinical cases is demonstrated. In addition, this article describes how SERS-based sensors work, addresses its advancements in the last 20 years, discusses its applications for detecting Coronavirus Disease 2019 (COVID-19), and finally describes future works. The authors hope that this article will be useful for researchers who want to enter this amazing field of research.

Keywords Surface-enhanced Raman spectroscopy · Nanosensor · Biological analytes · Chemicals · Metal nanoparticles · DNA · Cells · Tissues · Cancer · COVID-19

Introduction

The primary application of Raman spectroscopy is the identification of molecules. Nowadays, with the many advances made in the design of research equipment, Raman spectroscopy has become increasingly simpler, more accessible, and more cost-effective than before. By all means, despite these developments, interpretation of Raman spectra is still a major challenge and requires special skills. Similar to all spectroscopy methods, the Raman spectrum involves information about the electromagnetic waves that hit the sample. After the electromagnetic beam hits the molecule, part of it is scattered in all directions. Raman spectroscopy is used to observe vibrational, rotational, and other low-frequency modes in a system. This type of spectroscopy typically provides a special structural fingerprint that is applied to identify different molecules; this spectroscopy is also based on inelastic light scattering (called Raman scattering), monochromatic radiation, and monochromatic beams of laser light in the visible region, near-infrared light, or Raman that are usually close to ultraviolet light (Butler et al. 2016). Raman spectroscopy is one of the most important analytical methods for physical, chemical, and biological studies. The interaction of electromagnetic waves or photons with an atomic and molecular device can be as follows: (a) reflection of photons emitted from the surface of matter, (b) passage of photons through matter, (c) absorption of photons by matter molecules, and (d) incident light scattering from the surface of the material. The scattering of photons from matter occurs due to elastic and inelastic collisions, where no energy is exchanged between photons and molecules of matter due to elastic collisions, and only the path of motion

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of photons changes. However, in the inelastic collision, energy transfer is observed between the incident photons and the molecules of matter. Therefore, the Raman spectrum is due to the inelastic scattering of light from material molecules, which can be applied to obtain the vibrational spectrum of molecules, detect molecules, and acquire significantly detailed information about the molecular structure of materials. Since the Raman scattering spectrum is inherently weak and sometimes invisible and does not appear due to noise and the effect of fluorescence, this method is not appropriate to detect molecules with low concentrations, and it is necessary to amplify the Raman scattering spectrum. In this regard, Surface-Enhanced Raman Scattering (SERS) method is one of the most efficient methods for investigating low concentrations and detecting even a single molecule. In this method, metal nanoparticles are employed to enhance the Raman spectrum. In addition, SERS is a sensitive and selective method in which Raman scattering is increased for molecules adsorbed on metal nanoparticles. By applying this technique, in addition to analyzing molecular structures, some information about molecule adsorption and the process of molecules' interaction with the substrate's surface can be obtained (Wang and Fang 2006a). Due to the fact that the Raman scattering intensity is proportional to the square of the induced dipole moment, enhancement of this process is possible by "electric field enhancement" and "polarization enhancement" (Vo-Dinh 1998). When a molecule is close to the metal surface or physically absorbs metal nanoparticles, and due to the interaction of molecules and surface plasmons (mass movement of conducting electrons under the influence of incident wave oscillation field), a sharp increase in Raman signal occurs, which is known as the electromagnetic effect. In the other case, the molecule is chemically adsorbed on metal nanoparticles, and the Raman signal intensity increases due to the transfer of electrons from the metal to the molecule and their return to the metal. Some metals such as silver, gold, copper, and platinum have been used to observe the SERS phenomenon in various experiments (Canamares et al. 2008). Surface-enhanced Raman spectroscopy has grown rapidly over the past four decades and is rapidly expanding as diagnostic applications in the fields of chemistry, materials science, biochemistry, and life sciences. Advances in the fabrication of SERS-based biosensors are major breakthroughs in the detection of biological analytes and chemicals (Zong et al. 2018). Surface-enhanced Raman spectroscopy is one of the most sensitive analytical tools currently known; in some cases, it is possible to record a high-quality SERS spectrum in which even a single molecule is involved. Therefore, SERS is considered an extremely promising option as an alternative to routine analytical techniques used in food, environmental, biochemical, and medical analyses (Kneipp et al. 2008).

This review discusses the definitive and recent applications of SERS for the biochemical characterization of important compounds (especially medical and biological), direct and indirect manufacturing methods for the identification of biomaterials, the applications of biosensors, the mechanisms of SERS-based biosensor amplifiers and structures for the detection of biomolecules, as well as the theoretical foundations of the SERS effect, and describes how SERS-based sensors work, and finally discusses future applications of SERS in this field. The authors hope that this article will be useful for researchers who want to enter this amazing field of research.

In this review, the definitive and recent applications of SERS developed for the identification of biochemically important species (especially medical and biological) from the simplest to the most complex are briefly discussed. Moreover, the potential capability of SERS for being used as an alternative to routine methods in diagnostic and clinical cases is demonstrated. In addition, this article describes how SERS-based sensors work and finally discusses future works.

Properties of plasmon surface resonance in nanoparticles

In the Surface Plasmon Resonance (SPR) sensor, surface plasmon polaritons are excited at the interface of a thin metal film such as gold, silver, and dielectric. One of the factors that affect the surface plasmon oscillation of gold or silver nanoparticles is the effect of the refractive index of the environment in which the nanoparticles are located. A change in the refractive index of nanoparticles alters the emission constant of surface plasmons and causes some changes in the coupling between light and surface plasmon, which are visible as optical characteristics at the output (Kneipp et al. 2008; Sunmook 2007). This property is used to fabricate many sensors in the field of medicine and industry. The first high-sensitivity SPR sensor was developed in 1999 by Homola et al. (Homola et al. 1999) without the application of molecular labeling. The SPR biosensors have since been extensively used in the analysis of biomolecular interactions and the detection of chemical and biological analytes (Nooke et al. 2010; Homola et al. 2002; Koubová et al. 2001). With the advancement of the industry, the interest in the fabrication of sensors shifted to some sensors capable of sensing specific responses (due to targeted analyte molecules) from unspecified responses because of temperature fluctuations, analyte composition, and molecular absorption (Homola et al. 2005; Patskovsky et al. 2010). In later years, the development of multichannel sensors, such as prism coupled with SPR structure, was investigated for simultaneous measurement of different analytes (Hoa et al. 2007). Surface-enhanced Raman spectroscopy has grown increasingly over the past four decades and is rapidly expanding as applications for diagnostics in the fields of chemistry, materials science, biochemistry, and life sciences. Advances in the construction of SERS-based biosensors are major breakthroughs in the detection of biological analytes and chemicals (Zong et al. 2018).

Raman spectroscopy laser

Performance of Raman spectroscopy laser

Photons are often absorbed or scattered when they collide with a reflected molecule. In Raman spectroscopy, monochromatic radiation photons (single wavelength light) scatter in different directions after colliding with the sample. In this type of spectroscopy, the scattered photons of the sample are of great importance. Most of the photons that interact with the molecule are scattered elastically. This type of scattering is called Rayleigh scattering, in which the scattered photons of the sample have the same energy or wavelength as the photons that collide with the sample. In 1928, Chandrasekhara Venkata Raman, an Indian physicist, discovered a phenomenon called Raman. In this phenomenon, the energy or wavelength of the beam scattered by the molecules is different from the wavelength of the initial beam that collides the sample; this type of scattering of light beams is called inelastic scattering. Approximately one in ten million photons scatter inelastically after colliding with the matter. Moreover, the difference in energy or wavelength of scattered inelastic light depends on the molecular structure of the compound. In fact, Raman spectroscopy is on the basis of analyzing these differences and with the aim of determining the molecular structure of different compounds. The change in wavelength or energy of the initial radiation provides important information regarding the molecular movements within the system. In Raman scattering, a photon collides with the matter, and after scattering, its wavelength shifts to shorter or longer wavelengths. In this type of beam scattering, the transmission to higher wavelengths is predominant, which is called the Stokes Raman shift. Moreover, transmission to lower wavelengths is also called anti-Stokes shift (Downes and Elfick 2010; Nemecek et al. 2013). The intensity ratio of the anti-Stokes shift to Stokes has been reported to increase with increasing the temperature. The incident photon collides with the electron cloud of the functional group bonds, exciting the electrons to a virtual mode. Afterward, the electron returns from the virtual mode to an excited vibrational or rotational mode. This phenomenon causes the photon to lose a part of its energy and appear as a Stokes Raman shift. The lost energy is directly related to the chemical identity of the functional group, the molecular structure attached to it, the type of molecule's atoms, and its surrounding medium. Therefore, Raman spectra are specific to each molecule and can be used as a "fingerprint" in the chemical identification of molecular compounds in a liquid or air or on a surface (Nemecek et al. 2013; Loudon 1964).

Applications of Raman spectroscopy laser

Raman spectroscopy can be used in many fields, especially in any project that requires non destructive analysis, microscopy, chemical analysis, and imaging. Whether the study target is quantitative or qualitative information, Raman analysis can provide key information simply and rapidly. This technique is capable of quickly characterizing chemical compounds and samples with different phases such as solid, liquid, gas, gel, and powder (Prajapati and Prajapati 2011). Another pharmaceutical and criminology application of Raman spectroscopy is the high throughput characterization of drugs so that this technique can be used to analyze and report cocaine, heroin, ecstasy, and other phenethylamine ecstasy compounds at a considerably high speed and in a few seconds (Bell et al. 2000). In the field of antiquities research, each art object is unique, and sampling is usually prohibited, even if considerably small samples to be extracted in a few minutes. Since Raman spectroscopy usually does not require any sample preparation, it is considered a non destructive technique and is a suitable tool for archaeologists, especially researchers of artworks such as paintings, because this method can be applied to examine the pigments of paintings with high accuracy. In recent years, many articles have been reported on the applications of Raman microscopes for the analysis of pigment grains in manuscripts and paintings. In addition, this method has also been used to analyze ancient materials (Fig. 1) (Ziemann 2006), potteries (Fig. 2) (Sandalinas et al. 2006), and ancient glass beads (Fig. 3) (Welter et al. 2007). One of the most important non destructive applications of Raman spectroscopy is the analysis of biological samples. This type of analysis can detect cancerous tissues from healthy parts and identify cancer-prone cells. For instance, Kast et al. indicated that Raman spectroscopy is able to detect malignant tumors from a healthy breast sample and is also capable of detecting early neoplastic changes in mice (Kast et al. 2008). Since Raman signal measurements are often analyzed in conjunction with the properties of compounds, Raman spectroscopy is capable of analyzing complex compounds, including in vivo tissue analysis. Moreover, as the Raman signal can be obtained

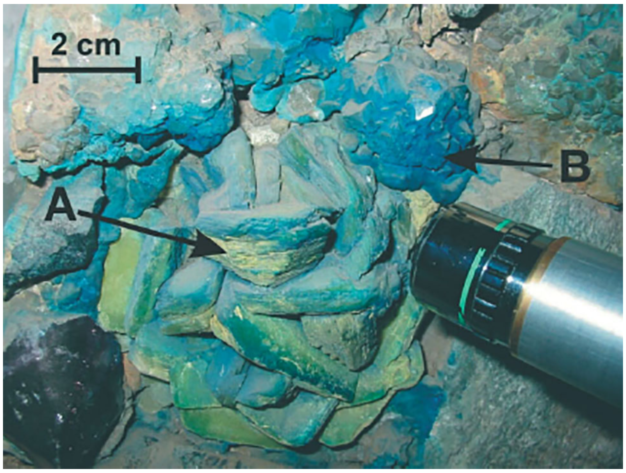

Fig. 1 Raman analysis of the yellow prussiate crystal and the blue layer on quartz on a group of pale greenish crystals of yellow prussiate located at a wall of the Grotto Hall. Reprinted from Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, Volume 37, Issue 10, Special Issue: Raman Spectroscopy in Art and Archaeology II, Martin A. Ziemann, In situ micro-Raman spectroscopy on minerals on-site in the Grotto Hall of the New Palace, Park Sanssouci, in Potsdam, Pages 1019–1025, Copyright 2006, with permission from John Wiley and Sons (Ziemann, 2006)

Fig. 2 An example of potteries analyzed by Raman spectroscopy; 'Albarello.' Venice, attributed to Domenego (1570–1580), majolica, height 18.4 cm, and maximum diameter 13 cm. Museo de Cerámica de Barcelona (MCB 1.222). Reprinted from Journal of Raman Spectroscopy, Volume 37, Issue 10, Special Issue: Raman Spectroscopy in Art and Archaeology II, C. Sandalinas, S. Ruiz-Moreno, A. López-Gil, J. Miralles, Experimental confirmation by Raman spectroscopy of a Pb-Sn-Sb triple oxide yellow pigment in sixteenth-century Italian pottery, Pages 1146–1153, Copyright 2006, with permission from John Wiley and Sons (Sandalinas et al. 2006)

Fig. 3 Ancient glass beads analyzed by Raman spectroscopy. Reprinted from Journal of Raman Spectroscopy, Volume 38, Issue 1, N. Welter, U. Schüssler, W. Kiefer, Characterisation of inorganic pigments in ancient glass beads by means of Raman microspectroscopy, microprobe analysis and X-ray diffractometry, Pages 113–121, Copyright 2007, with permission from John Wiley and Sons (Welter et al. 2007)

using a small probe, the optical fiber can be used as a probe. This feature makes it possible to move and carry the spectrometer easily or to test a Raman sensor inside the animal's body. Some important potential applications for the Raman effect are related to the different techniques of this effect, each of which has many applications in different fields. Moreover, the cheapness and smallness, and simple use of this type of spectrometer have made this technique interesting for scientists and researchers of different sciences (Vo-Dinh 1998). Raman spectrum is the inelastic scattering of light from molecules (Fig. 4), which can be used to obtain the vibrational spectrum of molecules, thus identifying molecules and obtaining significantly detailed information about the molecular structure of materials.

Advances of Raman spectroscopy laser

Raman spectroscopy has made many advances in recent years, some of which are mentioned in this section. Li et al. investigated Raman spectroscopy to detect adulterant substances such as high fructose corn syrup (HFCS) and maltose syrup (MS) used in natural honey. The main purpose of their study was to investigate the potential application of Raman spectroscopy to distinguish between pure honey and adulterated honey mixed with HFCS or MS, and interestingly they concluded that Raman spectroscopy combined with partial least squares-linear discriminant analysis (PLS-LDA) was effective in this regard (Li et al. 2012). One year later, Uysal et al. used Raman spectroscopy to detect adulterated butter with margarine. This investigation aimed to evaluate the performance of Raman

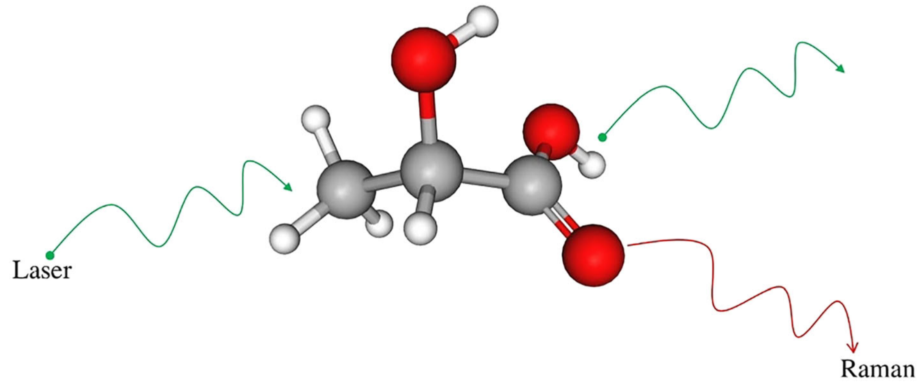

Fig. 4 Scattering of light from a molecule

spectroscopy in comparison with other identification devices, such as principal component analysis (PCA), principal component regression (PCR), partial least squares (PLS), and artificial neural networks (ANNs). Consequently, Raman spectroscopy was considered a quick tool for detecting adulterated butter with margarine when compared with other devices (Uysal et al. 2013). In addition, Perez et al. applied Raman spectroscopy to identify Huanglongbing (HLB) on plants and citrus. They found that Raman spectroscopy can be considered as a fast and cost-effective method to determine which plants, whether symptomatic or asymptomatic, are HLB positive or not (Pérez et al. 2016). Early and rapid detection of pathogens in food and agricultural products to improve their nutritional value and food safety prevents economic losses and health-related problems. Raman spectroscopy seems to be a suitable alternative to time-consuming, destructive, and expensive diagnostic devices and is a fast, non destructive, low-cost, fingerprint-based technique used to identify biological materials and pathogens. In this regard, Mandrile et al. used Raman spectroscopy combined with chemometric analysis to monitor tomato infection by two dangerous and different viral pathogens, namely tomato yellow leaf curl Sardinia virus (TYLCSV) and tomato spotted wilt virus (TSWV) (Fig. 5). In this study, inoculated plants were experimentally monitored for 28 days in terms of incidence of symptoms, and in addition to measuring the amount of virus using real-time PCR, it was evaluated with a Raman spectroscopy device at the same time. Raman spectroscopy was used to detect inoculated (healthy) plants from virus-infected specimens, indicated that this method was suitable for early detection of viral infections of food and agricultural products (Mandrile et al. 2019).

Despite some advances in this field, the Raman scattering spectrum is inherently weak and sometimes invisible and does not appear due to noise and the effect of fluorescence. Therefore, this method cannot be ideal for detecting molecules with considerably low concentrations, and it is necessary to be amplified. The SERS method is one of the most efficient methods for studying low concentrations and detecting even a single molecule, discussed in the following sections.

Surface-enhanced raman spectroscopy laser

In the 1970s, it was observed that the Raman signals generated by molecules adsorbed on some nanostructured materials were significantly increased. The surface-enhanced Raman spectroscopy (SERS) is a sensitive and selective method in which Raman scattering is increased for molecules adsorbed on metal nanoparticles. By applying this method, in addition to analyzing molecular structures, some important information can be obtained about the absorption of the molecule and the process of interaction of the molecule with the substrate surface (Fig. 6) (Wang and Fang 2006b; Fikiet et al. 2018) All theories related to SERS can be divided into two electromagnetic and chemical effects. This phenomenon is the result of a synergistic mechanism based on (a) excitation of surface plasmons of nanoparticles and (b) chemical interactions. When nanostructures composed of materials interact with an electromagnetic wave with a real negative dielectric constant and a small hypothetical positive dielectric constant at a given excitation frequency (e.g., gold, silver, and copper), mass oscillations of surface conducting electrons (called surface plasmons) occur, creating an additional electric field in the vicinity of the illuminated nanostructure. In the case of homogeneous plasmonic nanostructures, the strongest increase in the electromagnetic field occurs in sharp areas and edges. In addition, regarding the agglomerates or masses of plasmonic nanostructures, a significantly large field increase is observed in the gaps between the nanoparticles, which are called "hot spots." In SERS, the increase in Raman signal output is approximately proportional to the fourth power of the field increase (Aroca 2006; Kudelski 2009); hence, significantly large SERS amplification factors can be obtained, making SERS spectroscopy one of the most sensitive analytical tools. The chemical mechanism of SERS involves the hybridization

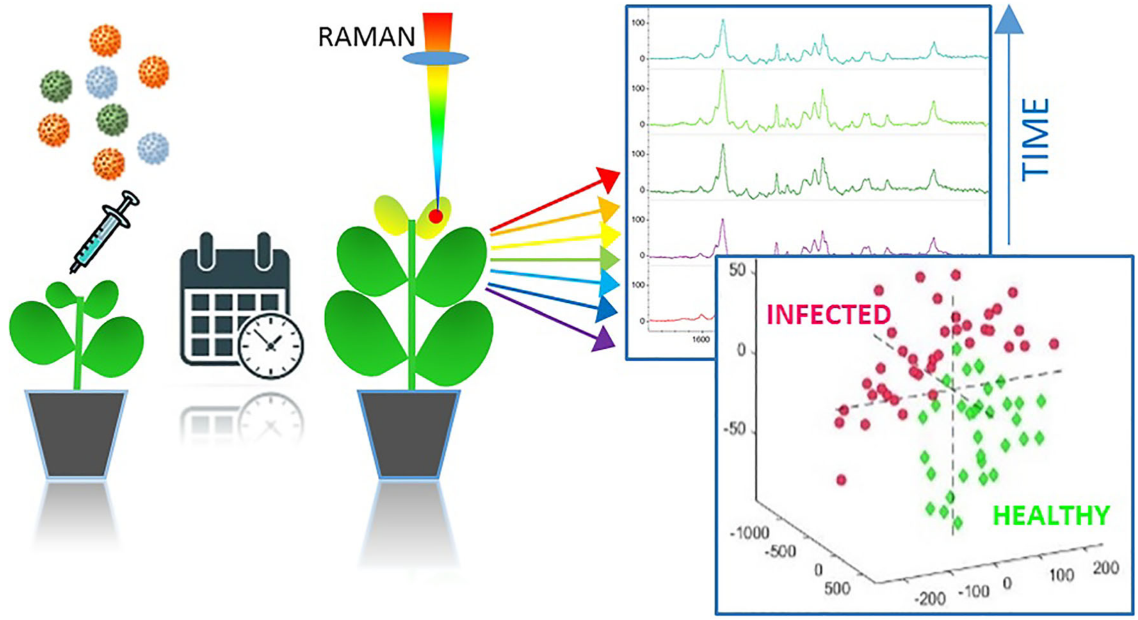

Fig. 5 A platform based on Raman spectroscopy combined with chemometric analysis to monitor tomato infection by two dangerous and different viral pathogens, namely tomato yellow leaf curl Sardinia virus (TYLCSV) and tomato spotted wilt virus (TSWV). Reprinted with permission from (Mandrile et al. 2019). Copyright 2019 American Chemical Society

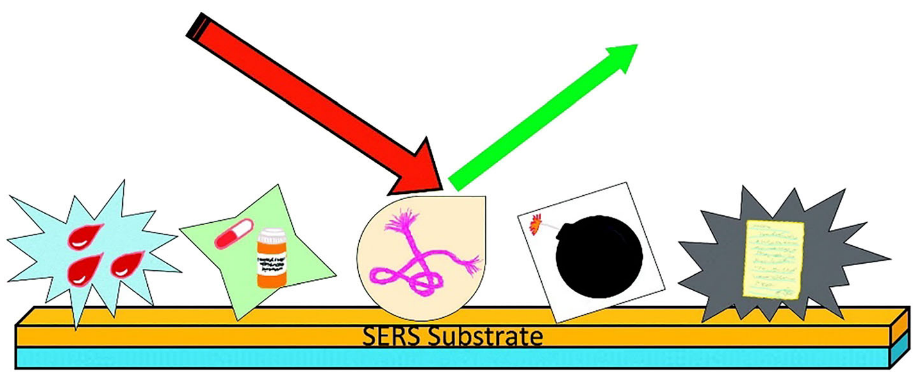

Fig. 6 A schematic of the application of SERS active substrates to detect biological and chemical materials. Reprinted from Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, Volume 197, Marisia A Fikiet, Shelby R Khandasammy, Ewelina Mistek, Yasmine Ahmed, Lenka Halámková, Justin Bueno, Igor K Lednev, Surface enhanced Raman spectroscopy: A review of recent applications in forensic science, Pages 255–260, Copyright 2018, with permission from Elsevier (Fikiet et al. 2018)

of the orbitals of adsorbed molecules with metal orbitals that facilitate the scattering of Raman resonances. The chemical mechanism is only important for molecules that interact directly with the metal surface and therefore does not usually work in SERS sensors. This technology has shown many advantages in high-sensitivity spectroscopy and fluorescence repulsion. The SERS method has been used until the present time to obtain information from molecules adsorbed on the surface of gold, silver, and noble metals. The detection of SERS not only increases the sensitivity of Raman scattering detection but can also provide information about the absorption direction of the molecule and the process by which the molecule interacts with the substrate surface, which is considered in some studies (Dieringer et al. 2006; Virga et al. 2013; Otto 2005; Qian and Nie 2008; Stranahan and Willets 2010).

Mechanism of metal nanostructures for sensitivity and amplification of surface-enhanced Raman spectroscopy laser

The SERS method is now used to obtain information from molecules adsorbed on the surface of gold, silver, and noble metals. Currently, the SERS enhancement is known for the reasons of two main phenomena: (1) The electromagnetic effect (field effect) in which the molecule is exposed to an external field; this larger alternative field is created by electromagnetic amplification near the metal surface, (2) chemical effect (molecular effect) in which molecular polarization is affected by the interaction between the surfaces of the molecule and the metal (Dieringer et al. 2006). By applying SERS, it is even possible to investigate single molecules that amplify the Raman signal up to 10^{10} through binding nanoparticles to single molecules (Qian and Nie 2008; Stranahan and Willets 2010; Ochoa et al. 2017; Ru et al. 2006). Consequently, the detection of biological substances in small quantities and their early detection are of great importance. Currently, several methods are used to quantify biomaterials, such as electrochemistry (Li et al. 2014), gas chromatography, High-Performance Liquid Chromatography (HPLC) (Heidbreder et al. 2001), gravimetry (Fourati et al. 2014; Maouche et al. 2015), and optical spectroscopy (Qian and Nie 2008; Stranahan and Willets 2010; Ochoa et al. 2017; Ru et al. 2006). These methods are destructive, challenging, polluting, in-laboratory, time-consuming, and expensive, as well as require sample preparation, trained specialists, and well-equipped laboratories. Therefore, it is essential to develop a non destructive method, simple to use, fast, cost-effective, unpolluted, portable, and applicable outside the laboratory environment that needs less sample preparation. On the other hand, the detection of significantly low amounts of biological analytes and chemicals is of great importance. Materials and biological analytes can be detected using infrared spectroscopy and Raman spectroscopy, both of which are fingerprint spectroscopies and used for studying the molecular vibrations of matter (Ivanov et al. 2002; Alizadeh 2009). In infrared spectroscopy, due to the active molecular vibrations of water, biological species are difficult to detect, and the sensitivity of their detectors is low. In Raman spectroscopy, due to the inherent weakness of the signal from Raman scattering, the study of molecules with low concentrations is practically impossible (Duan et al. 2016). One of the methods that can enhance the Raman signal is the use of metal nanostructures that can create a strong electric field near the nanostructures due to the intensification of surface plasmons or effectively improve the scattering signal by increasing the light scattering from these nanostructures, which will be followed by molecular vibrations with better and higher signals. The SERS is a sensitive and selective method that results in enhanced Raman scattering of molecules that are adsorbed on metal structures (Wang and Fang 2006b). Moreover, by irradiating light (laser) to a rough metal surface, enhanced electric fields are created around the metal by intensifying the surface plasmons of metal nanostructures by the electromagnetic field of laser (Ren et al. 2007; Matricardi et al. 2018), as if the electric field resulted from laser light radiation is amplified. Therefore, the molecule placed in this amplified electric field becomes more polarized, resulting in an enhanced Raman signal (Lin et al. 2016) In this method, when the target biological analytes and chemicals are placed near the metal surface or physically adsorb the metal nanoparticles, the intensity of the Raman signal increases due to the interaction of biological analytes and chemicals and metal surface plasmons; hence, SERS can be applied for rapid and accurate detection of microbiological analytes. Enhancement of the electromagnetic field in the plasmonic resonance mode of the nanoparticles increases the excitation and emission of enhanced Raman in the SERS mode. In metal nanoparticles, such as gold nanoparticles, silver nanoparticles, and nanoparticles of noble metals that have appropriate morphology and dimensions, the electromagnetic enhancement can be increased by a high factor called the hot spot, which is directly related to the increased sensitivity and amplification of SERS. Furthermore, nanostructured arrays can usually be adjusted so that many hot spots to be placed on them (Lin et al. 2016; Radziuk and Moehwald 2015) to enhance the sensitivity of SERS-based nanosensors and plasmonic resonance.

Surface-enhanced Raman spectroscopy laser as a biological sensor for the detection of biomaterials

In recent years, the surface plasmon of nanoparticles has received much attention from researchers due to its rapid response and high resolution in sensors. Noble metal nanoparticles, especially gold and silver, show unique optical properties in the calculation of surface plasmon resonance, which have received much attention in the electronics industry and in biochemical and medical applications. When the particle size reaches the nanometer level, a strong absorption is observed in the visible region, which is due to the intensification of the surface plasmon occurring in the visible UV spectrum and used to design chips and biosensors. Surface plasmon resonance is an appropriate tool for describing biomolecular interactions and is extensively applied in biosensors. Gold nanoparticles are employed to distinguish cancer cells from healthy ones. The purpose of this nanoparticle is to increase the adsorption of diseased cells in comparison with that of healthy cells. The width and position of the plasmon resonance peak depend on the size, shape, type of metal, the surrounding dielectric environment, and the distance between the nanoparticles, which is defined as the shift of the surface plasmon resonance peak over the visible spectrum. Moreover, surface plasmon resonance occurs when the frequency of incident light to metal nanoparticles is equal to the frequency of surface plasmon. In addition to the particle size, the adsorption peak of surface plasmon resonance of nanoparticles also depends on the environment of nanoparticles, and by changing the refractive index of the environment, the shift of surface plasmon resonance peak appears, which is used to design chemical and biological sensors (Toshima and Yonezawa 1998; You et al. 2007; Jain et al. 2007; Chen et al. 2007; Sarkar et al. 2009; Petrova et al. 2007). Some films composed of noble metal nanoparticles (typically gold and silver Ag) are now significantly popular and interesting in scientific research in nanotechnology due to their remarkable optical properties and the intensification of surface plasmons. When the electrons are shifted from their equilibrium positions, conduction electrons in noble metal nanoparticles lead to an increase in light and have potential applications in different fields such as biosensors (Shrivastava and Dash 2010; Krasteva et al. 2002) designing solar cells (Wu et al. 2012), and SERS (McLellan et al. 2007). Due to the excellent optical properties of noble metal nanoparticles, many existing methods for fabricating SERS biosensors have been proposed in recent years (Yu et al. 2011); such methods can be used as SERS biosensors. Since Raman spectroscopy does not face the same problems as other spectroscopies, it is extensively applied as a complementary method. For instance, in IR spectroscopy, due to the active molecular vibrations of water, it is difficult to detect biological species, and the sensitivity of its detectors is low. Compared to electron and ion-based spectrometers that require high vacuum, Raman spectroscopy not only allows molecular investigation under normal conditions, it can also be applied to examine catalytic processes and some procedures occurring at the metal–electrolyte interface (Wu et al. 2012). In 1974, the SERS phenomenon was first observed in the electrochemically cultured pyridine molecule adsorbed on the surface of silver electrodes. Raman spectrum related to 6.25 mM solution of pyridine in silver colloidal solution in comparison with 0.1 M solution as well as amplification of Raman lines could be observed (Fleischmann et al. 1974). In some experiments where the surface roughness of the electrode was as low as possible (a surface increase of approximately 10 times), an increase in Raman signal intensification was observed (Michaels 2000). Over the last few decades, some metals such as gold, silver, copper, and platinum have been applied to observe the SERS phenomenon in various experiments. Successful application of metal nanoparticles in SERS depends on some properties of the metal, such as morphology (shape, size, and mass) and the nature of the metal used, which was used as a substrate. Among the various metals, silver and gold have been mostly applied due to their wide plasmon resonance in the Vis–NIR region, high stability, and simple preparation procedure (Zhang et al. 2005). In this method, metal nanoparticles are employed to enhance the Raman spectrum. In fact, SERS is a sensitive and selective method in which Raman scattering is increased for molecules adsorbed on metal nanoparticles. In this regard, gold and silver surfaces are mostly employed due to their high stability (Sharma et al. 2012). In addition, substrates and various methods were used to fabricate active SERS substrates to rapidly and accurately examine biological and chemical samples; these substrates were fabricated by physical and chemical methods (Li et al. 2010; Betz et al. 2014). By employing the SERS biosensor, biological species and materials can be easily detected (Zhou et al. 2014). Various techniques such as HPLC (Cheng et al. 2011), Tandem Mass Spectrometry (TMS) (Banta-Wright and Steiner 2004), Gas Chromatography–Mass Spectrometry (GS–MS)] (Escobar-Morreale et al. 2012), amperometry (Njagi et al. 2010), chromatography (Phillips 1996), magnetic resonance spectroscopy (Kondo et al. 2011), and SERS have been used for the measurement of biomaterials and molecules (Ochoa et al. 2017). In addition to analytical sciences, SERS can be used in biomedicines, study of vitamins (Cañamares et al. 2008), biomolecules, viruses and bacteria (Pavel et al. 2008), analysis of explosives (Jerez-Rozo et al. 2008), detection of drugs (Li et al. 2009), and geology (Fig. 7) (Muniz-Miranda et al. 2009).

Surface-enhanced Raman spectroscopy laser for medical applications

The DNA, (Pyrak et al. 2019) RNA (Fig. 8) (Lee et al. 2019), cancer markers (Fig. 9) (Choi et al. 2020), bacteria (Andrei et al. 2021) viruses (Chen et al. 2020), genes (Vo-Dinh et al. 2002), drugs (Jaworska et al. 2016), pathological markers on membranes and cell tissues (Wallace and Masson 2020), other biomolecules, ion concentration, and redox potential in cells (Jaworska et al. 2021), and even in situ SERS monitoring of PH changes in phosphate-buffered saline and living cells (Fig. 10) (Wen et al. 2020) are all analyzed using surface-enhanced Raman spectroscopy. In many cases, the outcomes are at a level of diagnosis that is not obtainable by other analytical techniques. Raman spectroscopy, along with other basic biochemical techniques including UV–VIS spectroscopy, fluorescence, and PCR, is still used. Recent experiments show the ability of this method, and in some cases, SERS spectroscopy may be done effectively (generally) on medical samples. Chemical and biological SERS sensors, particularly DNA/RNA sensors that can detect cancer-related DNA mutations as well as bacteria and viruses, are projected to become much more developed. Furthermore, some food items may be validated using DNA sensors designed for medicinal uses. Although several SERS biosensors have been produced, many factors, such as the

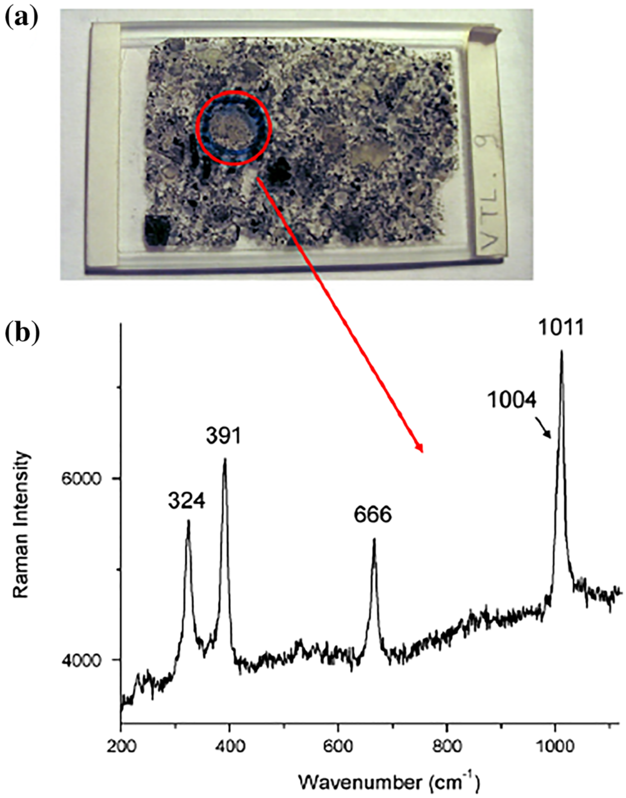

Fig. 7 Surface-enhanced Raman spectroscopy (SERS) applied for identifying **a** the clinopyroxene crystal as shown by the red circle. **b** The corresponding Raman spectrum measured exciting at 785 nm. Reprinted from Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, Volume 73, Issue 3, Maurizio Muniz-Miranda, Cristina Gellini, Luca Bindi, Surface-enhanced Raman spectroscopy for identifying rock composition, Pages 456–459, Copyright 2009, with permission from Elsevier (Muniz-Miranda et al. 2009)

reproducibility of SERS substrates, need to be improved before they can be commercialized. Surface-enhanced Raman spectroscopy is a possible alternative to many of the conventional analytical methods used in medical, biochemical, and biological investigations (Szaniawska and Kudelski 2021).

Direct and label-free detection of biomaterials using surface-enhanced Raman spectroscopy laser

Only direct adsorption of the investigated material onto the nanostructured plasmonic surface is required in the experimental method for label-free SERS detection. However, due to the weak signal-to-noise ratio and minor differences between the acquired spectra, analysis of the acquired spectra is usually difficult (e.g., the spectrum of healthy and cancerous cells or different types of bacteria). Although this technique is more particular than the nanosensor-based approach, when combined with improved data analysis, it offers extremely promising outcomes. Measurement of the patient's urine to identify and screen for the risk of recurrent prostate cancer (Fig. 11) (Ma et al. 2021), describing Hepatitis C Virus (HCV) RNA extracted from different blood samples from patients with HCV infection (Nasir et al. 2021), diagnosis of ulcerative colitis in blood plasma (Tefas et al. 2021), and assessment of the effectiveness of antiplatelet therapy (Zyubin et al. 2020) are some recent examples of label-free SERS applications. Unfortunately, in label-free studies, finding a new band that separates two sets of samples is very challenging. Chemometrics, on the other hand, may reveal small changes in the intensity or relative form of the band. The SERS is among the most sensitive methods for identifying substances at the atomic level, such as neurotransmitters, and has substantial advantages over traditional approaches (Lee et al. 2021). The rapid SERS-based approach of label-free dengue virus detection in blood samples (Fig. 12) (Gahlaut et al. 2020) is also an amazing example of a rapid SERS-based technique that needs only a small sample (5 μL). The label-free technique, on the other hand, is hampered by the fact that not all alterations in a

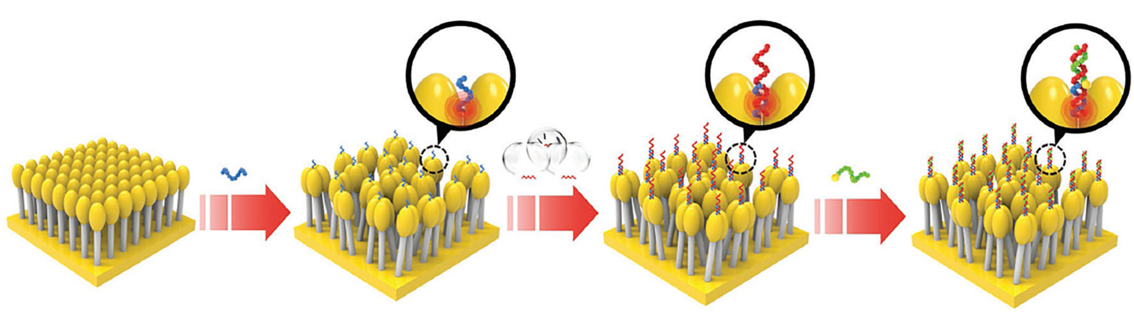

Fig. 8 Schematic illustration of exosomal miRNA detection using the SERS sensor based on a plasmonic gold nanopillar substrate. Reprinted from Small, Volume 15, Issue 17, Jong Uk Lee, Woo Hyun Kim, Hye Sun Lee, Kyong Hwa Park, Sang Jun Sim, Quantitative and Specific Detection of Exosomal miRNAs for Accurate Diagnosis of Breast Cancer Using a Surface-Enhanced Raman Scattering Sensor Based on Plasmonic Head-Flocked Gold Nanopillars, Copyright 2019, with permission from John wiley and Sons (Lee et al. 2019)

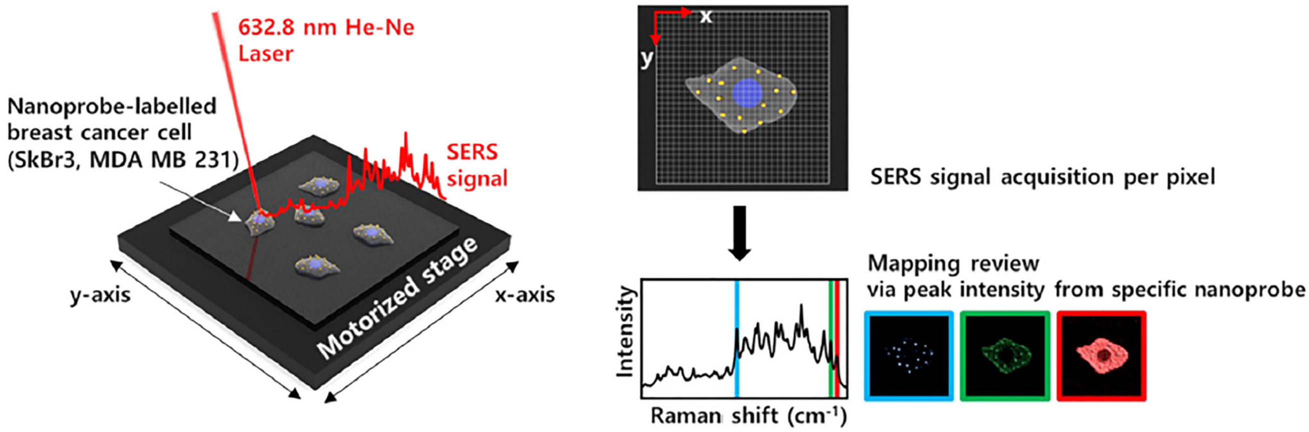

Fig. 9 Schematic illustration for simultaneous detection of three different breast cancer biomarkers using SERS technique. Reprinted from Biosensors and Bioelectronics, Volume 164, Namhyun Choi, Hajun Dang, Anupam Das, Myeong Seong Sim, Il Yup Chung, Jaebum Choo, SERS biosensors for ultrasensitive detection of multiple biomarkers expressed in cancer cells, Copyright 2020, with permission from Elsevier (Choi et al. 2020)

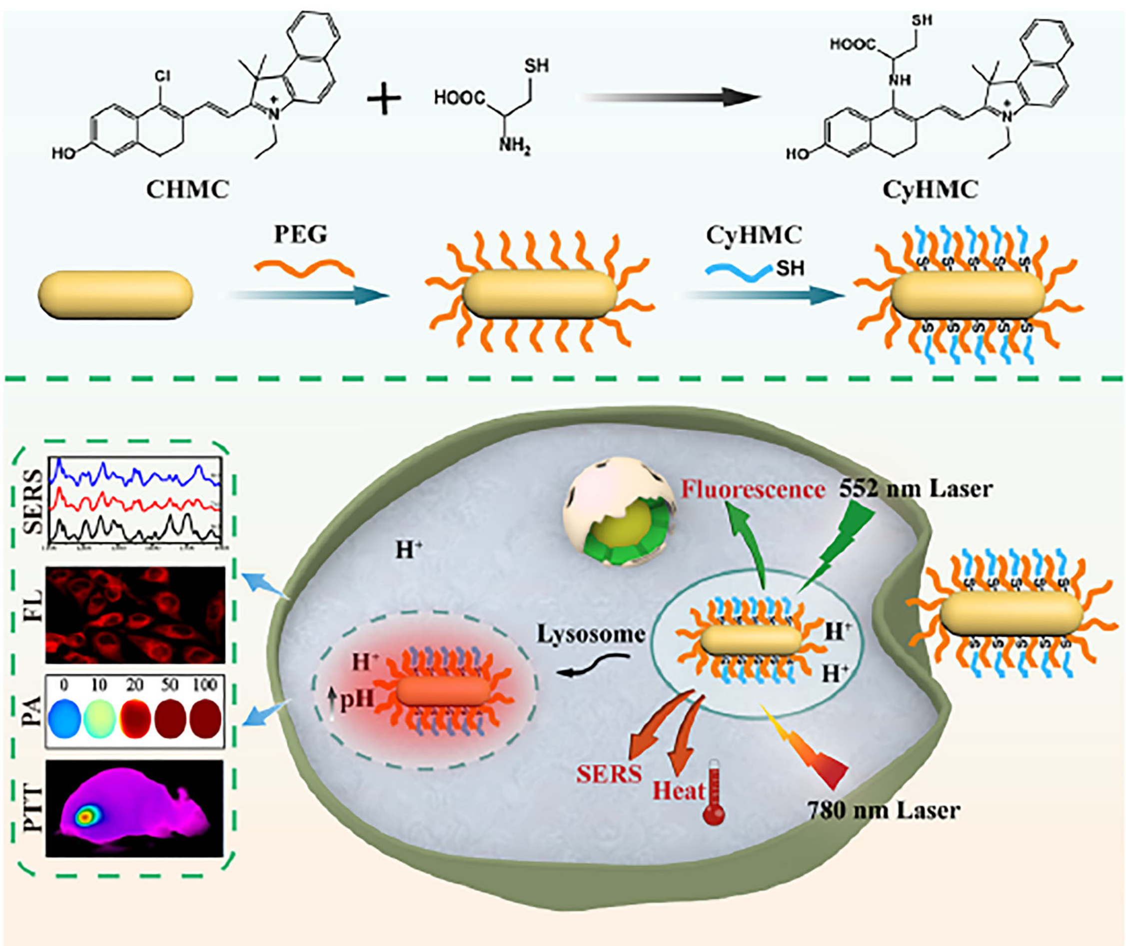

Fig. 10 Schematic diagram of the preparation of lysosome-targeted gold-based nanotheranostics for in situ SERS monitoring. Reprinted with permission from (Wen et al. 2020). Copyright 2021 American Chemical Society

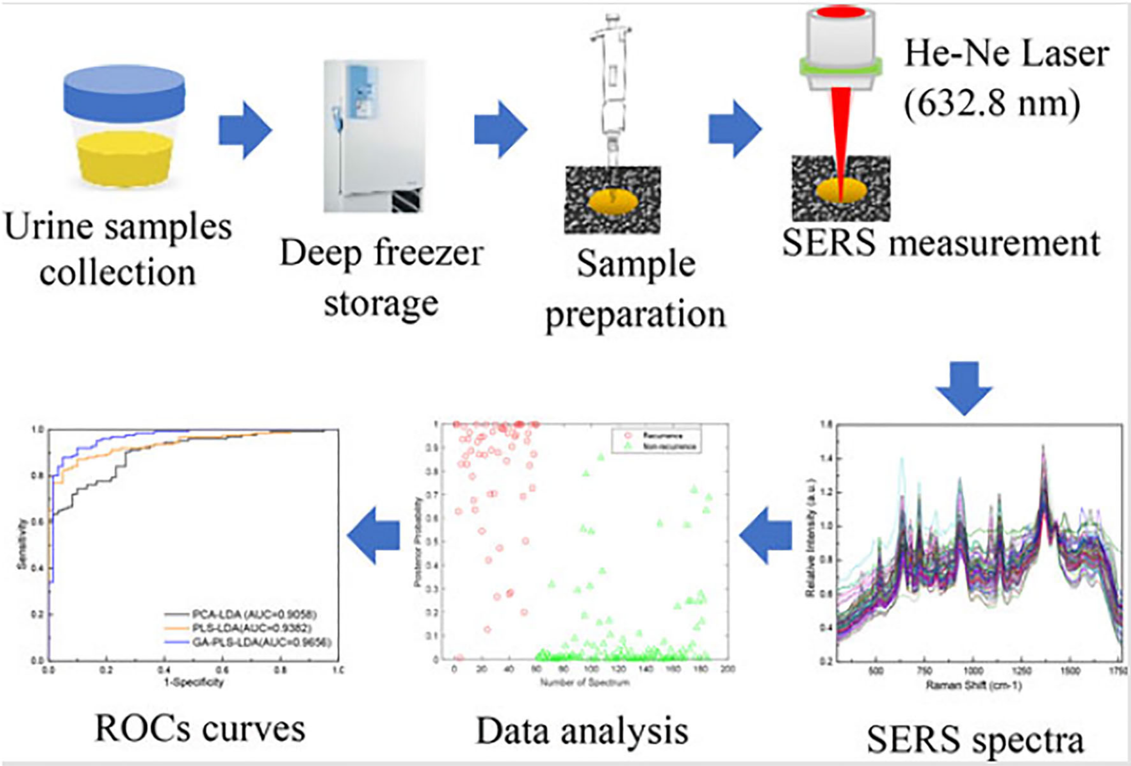

Fig. 11 Schematic illustration of the steps from urine samples preparation to data analysis of SERS spectra for prognosis of prostate cancer. Reprinted from Journal of Biophotonics, Volume 14, Issue 1, Yiwei Ma, Jingmao Chi, Zhaoyu Zheng, Athula Attygalle, Isaac Yi Kim, Henry Du, Therapeutic prognosis of prostate cancer using surface-enhanced Raman scattering of patient urine and multivariate statistical analysis, Copyright 2021, with permission from John Wiley and Sons (Ma et al. 2021)

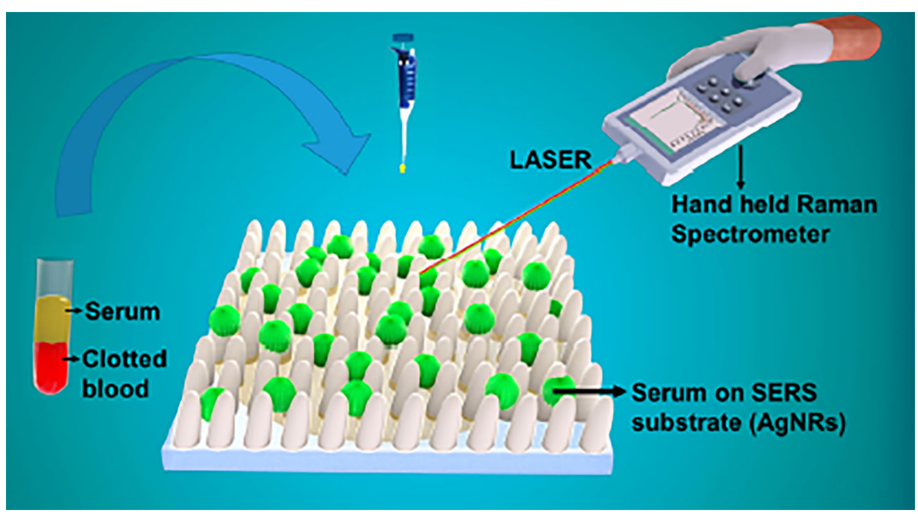

Fig. 12 Schematic illustration of a platform designed for detecting dengue virus in clinical blood samples. Reprinted with permission from (Gahlaut et al. 2020). Copyright 2020 American Chemical Society

sample's properties are linked to substantial spectral differences. As a result, rather than employing a simpler but less reliable label-free technique, one of the most potent approaches to introduce SERS to clinics is to develop sensors that can detect particular molecules with significantly low limits of detection.

Therapeutic drug monitoring using surface-enhanced Raman spectroscopy laser

Therapeutic Drug Monitoring (TDM) involves assessing the concentration of a medication in a biological matrix (usually plasma or serum) at a specific time related to the administration and interpretation of these concentrations based on relevant clinical parameters (target range and

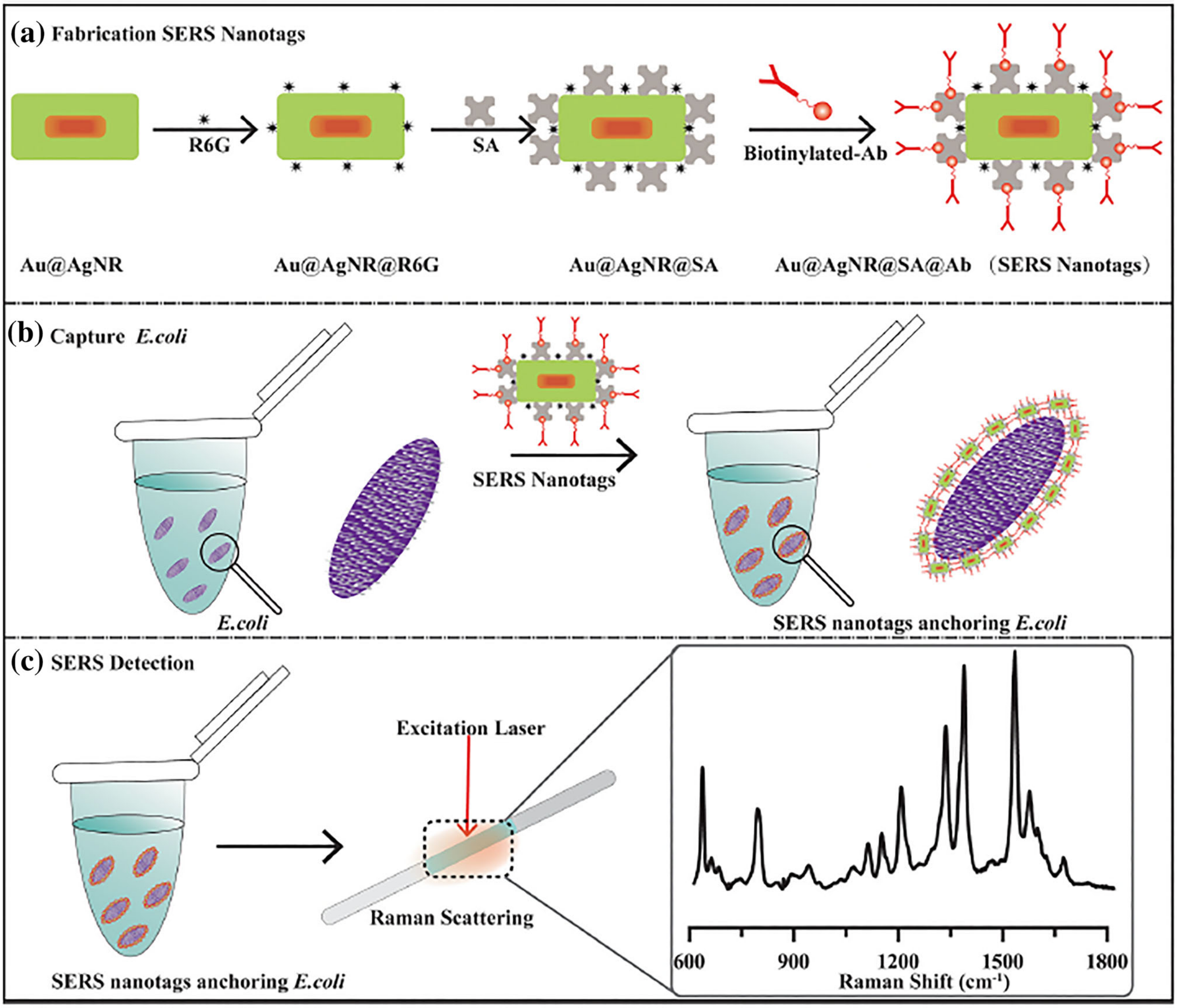

Fig. 13 Preparation of SERS nanotags and their attachment to *Escherichia coli*, Reprinted from Talanta, Volume 220, Liyan Bi, Xiao Wang, Xiaowei Cao, Luying Liu, Congcong Bai, Qingyin Zheng, Jaebum Choo, Lingxin Chen, SERS-active Au@Ag core–shell nanorod (Au@AgNR) tags for ultrasensitive bacteria detection and antibiotic-susceptibility testing, Copyright 2020, with permission from Elsevier (Bi et al. 2020)

pharmacokinetics of the medication) (Jaworska et al. 2016). In the TDM test, the simplest approach is to simply examine the recorded SERS spectra of body fluids (urine, blood, and blood plasma) that contain the drug and monitor the intensity of the bands assigned to that medication (Markina et al. 2020). Unfortunately, due to the complexity of the sample, this method requires some luck because the spectral symptoms of the drug, due to the interference of body fluid signals, are not necessarily observed in the recorded spectra. Therefore, a more common method is to combine SERS with extraction methods, such as liquid–liquid or solid phase extraction.

Detection of glucose using surface-enhanced Raman spectroscopy laser

Another topic of interest in medical diagnosis is glucose level screening. Nowadays, this procedure requires several daily blood measurements, which causes discomfort, pain, and the risk of infection. The development of a continuous and less invasive glucose screening device could have a major impact on 415 million diabetic patients worldwide. In this regard, a cost-effective SERS sensor was developed by Zhou et al. in 2020 for intradermal glucose detection (Ju et al. 2020). This sensor was calibrated in the range of 0–20 mM in dermal phantoms and successfully tested for

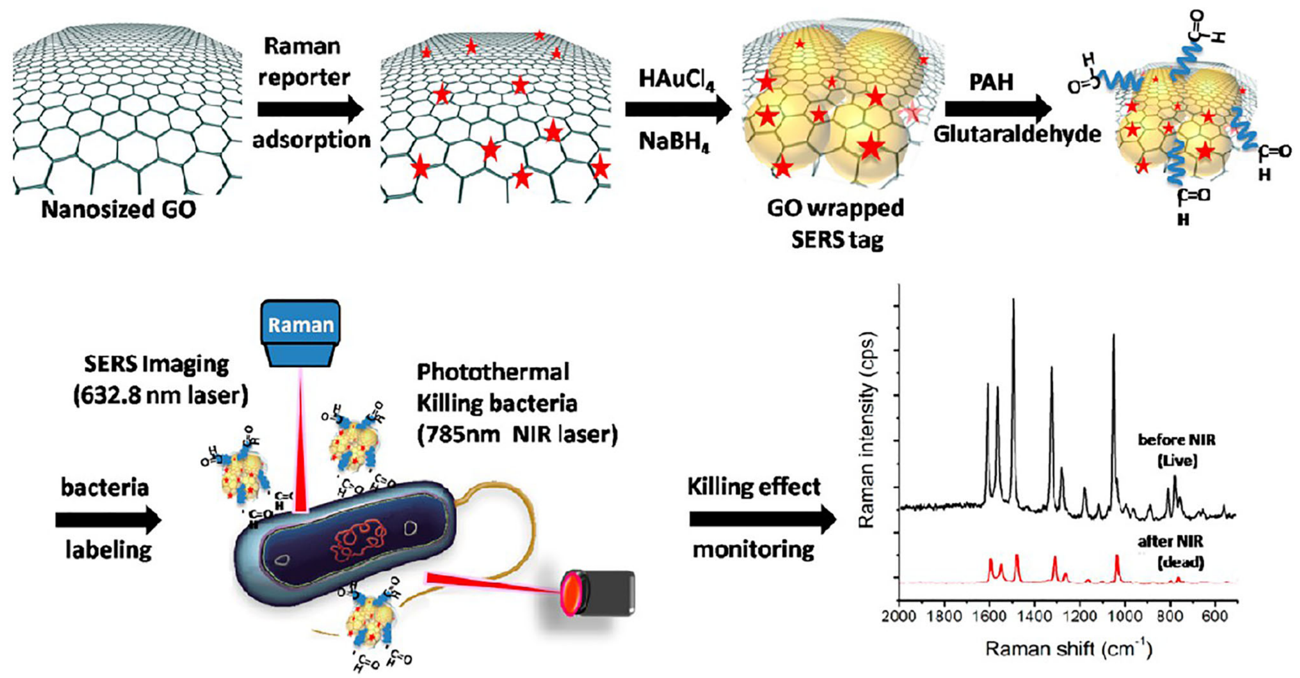

Fig. 14 Preparation of multifunctional, aldehyde group conjugated Au@Rubpy/GO SERS tags for detection of *Staphylococcus aureus* and *Escherichia coli*. Reprinted with permission from (Lin et al. 2014). Copyright 2014 American Chemical Society

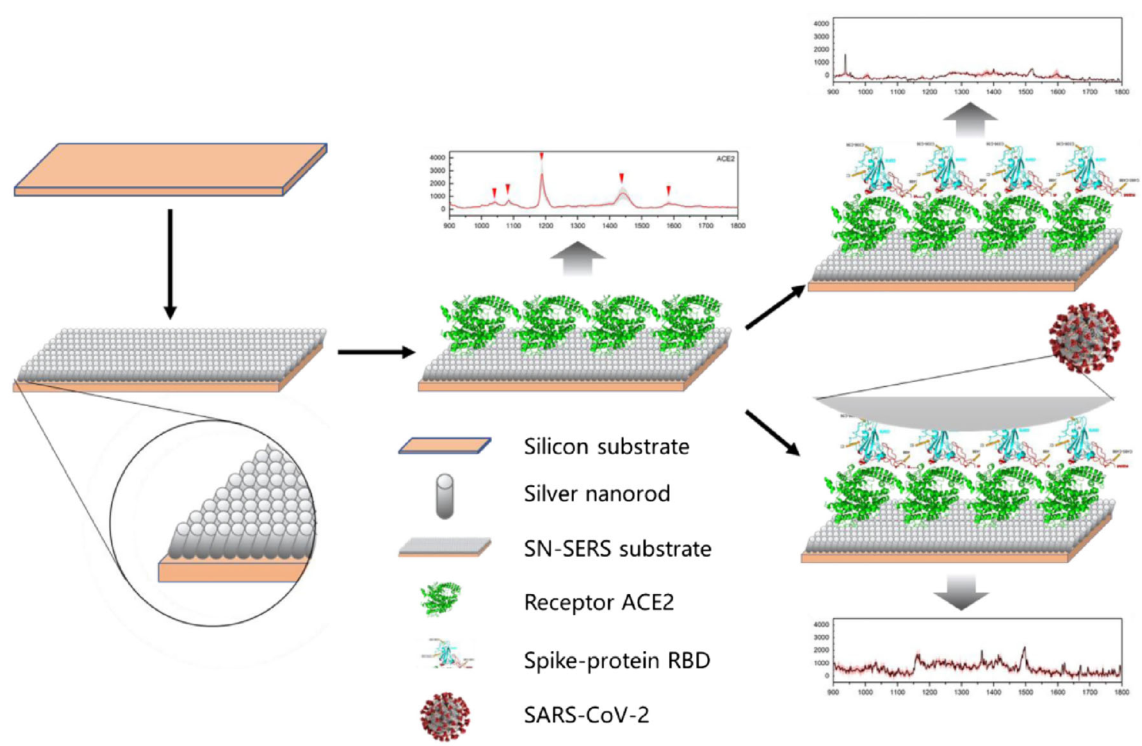

Fig. 15 State-of-the-art spectroscopic device for screening and interrogating SARS-CoV-2 with RBD for human cell entry by applying a silver nanorod SERS array functionalized with the cellular receptor angiotensin-converting enzyme 2 (ACE2). Reprinted from Water Research, Volume 200, Dayi Zhang, Xiaoling Zhang, Rui Ma, Songqiang Deng, Xinzi Wang, Xinquan Wang, Xian Zhang, Xia Huang, Yi Liu, Guanghe Li, Jiuhui Qu, Yu Zhu, Junyi Li, Ultra-fast and onsite interrogation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in waters via surface enhanced Raman scattering (SERS), Copyright 2021, with permission from Elsevier (Zhang et al. 2020)

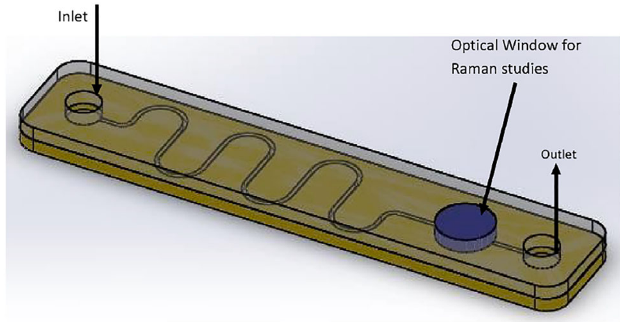

Fig. 16 Integrated microfluidic platform with vertically aligned carbon nanotubes (VACNTs) functionalized microchannel for detection of SARS-CoV-2. Reprinted from Medical Hypotheses, Volume 146, Siddhita A. Jadhav, Pullithadathil Biji, Manoj Kumar Panthalingal, C Murali Krishna, S Rajkumar, Dattatraya S.Joshi, Natarajan Sundaram, Development of integrated microfluidic platform coupled with Surface-enhanced Raman Spectroscopy for diagnosis of COVID-19, Copyright 2021, with permission from Elsevier (Jadhav et al. 2021)

in vivo glucose characterization in a streptozotocin-induced type-I diabetes mellitus mouse model.

Detection of bacteria using surface-enhanced Raman spectroscopy laser

Another interesting example of the capability of SERS is the detection of bacteria. Bi et al. (Bi et al. 2020) developed a specific platform for the diagnosis of *Escherichia coli* and antibiotic susceptibility tests (Fig. 13). They used rhodamine 6G-modified silver-core gold-nanotubes to detect the bacteria at 10^2 CFU/ml to confirm the presence of bacteria in the blood of mice and to identify antibiotic resistance within only 3.5 h. Apart from the ultrasensitive detection of bacteria, the SERS-based approach can go further and kill the bacteria by the photothermal method. Lin et al. (2014) conjugated the bacteria with graphene oxide-modified labels (Fig. 14). The SERS detected both gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli*) bacteria and, in addition, destroyed them by photothermal approach, indicating the potential of SERS assay for in situ screening of the photothermal antibacterial response.

Diagnosis of COVID-19 using surface-enhanced raman spectroscopy laser

In recent years, the Coronavirus Disease 2019 (COVID-19) pandemic has created a challenging and complex situation in the world. Various methods are developed to detect the COVID-19; Reverse Transcription Polymerase Chain Reaction (RT-PCR) is currently the most widely available standard method for diagnosing the disease; however, this method is complex, costly, and time-consuming and involves preprocessing the samples. Therefore, a fast and low-cost diagnostic protocol with high sensitivity for mass screening seems crucial to combat this pandemic and probable epidemic conditions in the future.

Since SERS has shown its capabilities in this regard, some investigations have been carried out with the aim of developing SERS-based biosensors to detect COVID-19. Tadesse et al. declared that with the development of SERS platforms, machine learning, microfluidics, and bioprinting, a combination of concepts can be integrated into an integrated and advanced platform to accelerate the diagnosis of COVID-19 (Tadesse et al. 2020). For the identification of SARS-CoV-2-specific IgM/IgG in serum of COVID-19 patients, Srivastav et al. (Yadav et al. 2021) compared the performance of a traditional lateral flow assay (LFA) with a SERS-based LFA test. Rapid detection in serum utilizing a custom-built SERS scanner was at least an order of magnitude more sensitive than traditional LFAs. Furthermore, SERS detection has a sensitivity of seven orders of magnitude greater, with a LOD of about ca. 100 fg/mL compared to around ca. 1 g/mL for naked-eye detection. Zhang et al. (2020) applied a silver nanorod SERS array functionalized with the cellular receptor angiotensin-converting enzyme 2 (ACE2), and their findings established a state-of-the-art spectroscopic device for screening and interrogating viruses with RBD for human cell entry, demonstrating its suitability and great promise as an ultra-fast detection method for wastewater-based epidemiology (Fig. 15). Pramanik et al. (2021) used 4-aminothiophenol as a reporter molecule, which was attached to the gold nanoparticle via an Au–S bond, to demonstrate that antibody-attached gold nanoparticles bound to SARS-CoV-2 spike protein, preventing the virus from binding to cell receptors, stopping virus infection and spread, and also had the potential to destroy the virus's lipid membrane. Payne et al. (2021) used peptides as viral protein capture probes and designed an angiotensin-converting enzyme 2 (ACE2) mimetic peptide-based SERS sensor for SARS-CoV-2 with a 300 nM detection limit and high efficiency in the presence of a high concentration of bovine serum albumin. Moreover, Jadhav et al. (2021) presented a diagnostic protocol based on SERS coupled with microfluidic systems consisting of functionalized microchannels with carbon nanotubes coated with Au/Ag or disposable electrospinning nanofilms/microfilters (Fig. 16). If this device is successfully developed and proven to detect target viruses well, it could enable rapid and mass screening of symptomatic and asymptomatic COVID-19 patients and be used in possible pandemics in the future.

Given that SERS has experienced increasing progress in the last 20 years, to clarify the importance of research in this field in recent years, a summary of studies conducted

Table 1 A summary of studies conducted in recent 20 years for the detection or analysis of different materials using the SERS technique

References	Target materials	Methodology and platform	Nanoparticles used	Type of substrates	Limit of detection (LOD)
Payne et al. (2021)	SARS-CoV-2	An angiotensin-converting enzyme 2 (ACE2) mimetic peptide-based SERS sensor	Gold nanoparticles	Peptide functionalized substrates	300 nM
Pramanik et al. (2021)	COVID-19 viral antigen or virus	SERS	Gold nanoparticles	–	~ 4 pg/mL
Zhang et al. (2020)	SARS-CoV-2	An assay using surface-enhanced Raman scattering (SERS) coupled with multivariate analysis	Silver nanorod	ACE2@SN-SERS substrate	–
Nasir et al. (2021)	Hepatitis C Virus (HCV)	SERS	Silver nanoparticles	Silver nanoparticle-based substrate	2.55 log IU/mL
Wen et al. (2020)	PH changes in phosphate-buffered saline and living cells	A novel lysosome-targeted gold-based nanotheranostics for in situ SERS monitoring	Gold nanorods	–	–
Andrei et al. (2021)	*Staphylococcus aureus Escherichia coli*	SERS	Silver nanoparticles	Microscope glass slides	–
Jadhav et al. (2021)	SARS-CoV-2	A diagnostic protocol based on SERS coupled with microfluidic devices containing integrated microchannels	Ag/Au nanoparticles	–	–
Bi et al. (2020)	*Escherichia coli*	A SERS-active Au@Ag core–shell nanorod (Au@AgNR) tag platform	Au@AgNRs	–	10^2 CFU/mL
Ju et al. (2020)	Glucose	SERS detection based on functional polymethyl methacrylate microneedle (F-PMMA MN) array	Silver nanoparticles	Silver substrate	–
Gahlaut et al. (2020)	Dengue virus in clinical blood samples	SERS	Silver nanorods	Silver nanorods array	–
Zyubin et al. (2020)	Platelets obtained from patient specimens	SERS	Gold nanoparticles	Au/Ti SERS substrate	–
Tefas et al. (2021)	Plasma samples for diagnosis of ulcerative colitis (UC)	SERS	Silver nanoparticles	Solid plasmonic silver substrates	–
Ma et al. (2021)	Urine samples of 12 recurrent (Re) and 63 nonrecurrent (NRe) patient cohorts to assess the treatment response of prostate cancer (PCa)	SERS	Silver nanoparticles	SERS-active silicon substrate	–
Choi et al. (2020)	Three different biomarkers expressed in breast cancer cells (EpCAM, ErbB2, and CD44)	SERS nanotags	Cobalt nanoparticles	–	–
Lee et al. (2019)	Exosomal miRNAs	A SERS-based sensing platform	–	Plasmonic gold nanopillar SERS substrate	1 aM
Zhou et al. (2014)	Three strains of *Escherichia coli* One strain of *Staphylococcus epidermidis*	SERS	Silver nanoparticles	–	2.5×10^2 cells/mL

Table 1 (continued)

References	Target materials	Methodology and platform	Nanoparticles used	Type of substrates	Limit of detection (LOD)
Lin et al. (2014)	*Staphylococcus aureus Escherichia coli*	Multifunctional, aldehyde group conjugated Au@Rubpy/GO SERS tags	Gold nanoparticles	–	–
Muniz-Miranda et al. (2009)	Pyroxene grains embedded in polymorphous rock matrices	SERS	Silver nanoparticles	–	–
Li et al. (2009) (Li et al. 2009)	Morphine	SERS, infrared adsorption (IR), normal Raman (NR) scattering, density functional theory (DFT)	Silver nanoparticles	–	–
Jackeline I. Jerez-Rozo et al. (2008)	2,4,6-trinitrotoluene (TNT) in aqueous solution	UV–VIS spectroscopy, Scanning and Transmission Electron Microscopies, and SERS	Gold and silver nanoparticles	Gold and Gold/ Silver Colloids	–
Pavel et al. (2008)	Protein molecules	SERS	Silver nanoparticles	–	–
Vo-Dinh et al. (2002)	BRCA1 breast cancer gene BAX gene	DNA gene probes based on SERS labels (surface-enhanced Raman gene [SERGen] probes)	Silver nanoparticles	Silver-island films deposited on glass surfaces	–

from 2002 to 2021 to detect different materials using the SERS technique, separated by the methodologies, nanoparticles, substrates, and limit of detection (LOD), are listed in Table 1.

Conclusion

This review briefly discusses recent advances in the use of SERS to detect important biochemical species (particularly medical and biological). The chemical and biochemical SERS sensors, especially DNA/RNA sensors that can be applied to detect cancer-related DNA mutations and various bacteria and viruses, such as COVID-19, are expected to be increasingly developed. In addition, DNA sensors developed for medical applications can be used in other fields; for example, they can be applied to validate some food products. Although many SERS biosensors have been developed, many aspects, such as the reproducibility of SERS substrates, still need to be improved before commercialization. Raman spectroscopy method is based on receiving information from light scattering phenomenon while colliding with the matter. Nowadays, this method has many applications in various fields of research and provides important information regarding the structure of molecules so that Raman bands can be considered as a type of fingerprint for compounds. Since the Raman scattering spectrum is inherently weak and sometimes invisible and does not appear due to noise and the effect of fluorescence, it is not possible to detect molecules with low concentrations through this approach, and it is necessary to enhance the Raman scattering spectrum. Moreover, this technique is among the most efficient approaches for studying low concentrations and detecting even a single molecule. In this study, first, the theories of amplification mechanisms of SERS signal were briefly reviewed, and then the applications of SERS biosensors for the diagnosis of medical and biological analytes were investigated. This method provides an advancement in examining and diagnosing the disease in a non destructive manner. Furthermore, some nanoparticles such as gold, silver, and copper were introduced as Raman signal enhancers. Surface-enhanced Raman spectroscopy, after its discovery, was first used to investigate electrochemical reactions and adsorption of molecular species on metal surfaces. Due to its inherent molecular fingerprint properties and the potential to detect a single molecule, SERS has been an attractive tool for measuring molecules in small quantities in the field of chemical analysis. The fabrication of SERS active substrates is a new method for the detection of toxic substances, narcotics, industrial toxic chemicals, biological analytes, and the analysis of other biological and non-biological species at low concentrations due to the simplicity of the fabrication process, cost-effectiveness, and the capability of detecting materials at low concentrations. Finally, SERS has excellent applications in the field of detecting and diagnosing viral diseases, such as COVID-19, and SERS-based platforms can be developed to prevent probable epidemics in the future, or if being exposed to a condition similar to COVID-19 pandemics, they can be applied for rapid and ultrasensitive detection of viruses or other agents. The authors hope that the examples presented in this review convince readers that SERS spectroscopy is a promising option as an alternative to many of the routine analytical techniques used in medical, biochemical, and biological analyses.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

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