Detection of Heavy Metals in Food and Agricultural Products by Surface-enhanced Raman Spectroscopy

Zhiming Guo, Ping Chen, Nermeen Yosri, Quansheng Chen, Hesham R. Elseedi, Xiaobo Zou & Hongshun Yang

To cite this article: Zhiming Guo, Ping Chen, Nermeen Yosri, Quansheng Chen, Hesham R. Elseedi, Xiaobo Zou & Hongshun Yang (2021): Detection of Heavy Metals in Food and Agricultural Products by Surface-enhanced Raman Spectroscopy, Food Reviews International, DOI: 10.1080/87559129.2021.1934005

To link to this article: https://doi.org/10.1080/87559129.2021.1934005

Published online: 10 Jun 2021.
Detection of Heavy Metals in Food and Agricultural Products by Surface-enhanced Raman Spectroscopy

Zhiming Guo, Ping Chen, Nermeen Yosri, Quansheng Chen, Hesham R. Elseedi, Xiaobo Zou, and Hongshun Yang

School of Food and Biological Engineering, Jiangsu University, Zhenjiang, China; Pharmacognosy Division, Department of Medicinal Chemistry, Uppsala University, Biomedical Centre, Uppsala, Sweden; International Research Center for Food Nutrition and Safety, Jiangsu University, Zhenjiang, China; Department of Food Science & Technology, National University of Singapore, Singapore, Singapore

ABSTRACT

Heavy metals accumulating in the human body produce physiological toxicity by interfering with the transport of human proteins and enzymes. Heavy metals detection is significant for food safety assurance. This review focuses on recent advances of heavy metals detection of food and agricultural products by surface-enhanced Raman spectroscopy (SERS). The article covers the SERS basic principles and advances in heavy metals detection, including mercury, arsenic, cadmium, lead, chromium among others. Insights in the potential of combining chemometrics and multivariate analysis with SERS and the exploration of novel SERS substrate platforms from both macro and micro scale are discussed. Finally, future application of SERS in heavy metal detection are prospected. SERS is a powerful and promising technique offering the advantages of simple sampling, rapid data collection and non-invasiveness. The findings of this study can allow better understanding of the heavy metals' occurrence and the possibility of its detection using SERS.

KEYWORDS

Food safety; heavy metal; surface-enhanced raman spectroscopy; nanoparticles; chemometrics; substrate platforms

Introduction

Heavy metals are one of major potential substances of food contaminants and can be found in nature, industrial and environmental pollutants. Several hazardous heavy metals have already posed health hazards to humans seriously through the food chain due to the increased presence in food. Increasing expansion of commercial land and the rapid pace of industrialization are at the root of the problem, particularly in densely populated developing countries, such as China and India. Heavy metals are ubiquitous on earth, they are absorbed from soil pores by producer “plants” in the form of ions, which can vary by metal. The original data surveyed from the 5th China TDS showed the prime dietary sources of aluminum (Al), arsenic (As), cadmium (Cd), and chromium (Cr) is from cereals and vegetables, aquatic products are proved to be the major dietary source for mercury (Hg) and dietary exposure of lead (Pb) is from water, beverages, cereals, vegetables and meats. Eating foods contaminated with heavy metals links to an increasing number of human health issues, such as cancers of the digestive tract, mental retardation, and malnutrition. A study of health risks, focused on heavy metal–triggered cancer, showed that heavy metals with THQ values >1 in food crops include Cr, Pb, As and Cd. In addition, Pb is related to gastric and have been suggested to trigger liver cancers.

Assuring food safety and quality cannot be complied without effective analytical techniques. Heavy metals detection has become an urgent requirement for food raw materials such as grain, fruit, water, tea and other processed agro-products. Conventional methods such as atomic absorption
spectroscopy (AAS), atomic fluorescence spectrometry (AFS), inductively coupled plasma-mass spectrometry (ICP-MS) and other novel techniques, including imaging, spectroscopic imaging as well as chemical biosensors are accurate enough, but they all fail to meet the requirements for rapid and on-line detection by these technologies. Surface-enhanced Raman spectroscopy (SERS) has proven to be a very effective method for detecting trace amount of heavy metals in food (Fig. 1) due to its super sensitivity, quick response, and clear “fingerprint-like” details about characterization.

This review is a comprehensive comment about heavy metals detection in food and agricultural products using SERS. We will introduce the fundamentals of SERS and discuss its applications for heavy metals detection in food. Considering the breadth of the SERS field, also we will basically highlight the construction of novel SERS substrate platforms, Raman spectral data processing with chemometrics and heavy metals detection applications.

**Fundamentals of SERS**

**Principle of SERS**

Raman spectroscopy is a non-elastic scattering spectrum based on matter to light. SERS is obtained from the interaction between the molecules to be measured and rough metals such as copper, gold and silver, and increased Raman spectral strength by 4–7 orders of magnitude.

![Figure 1. Schematic representation of the surface enhanced Raman spectroscopy applied in detection of heavy metals in food and agricultural products with flexible substrate and chemometrics.](image-url)
As a particular system (Fig. 2), the signal strength of the surface elevated Raman spectra first depends on the size of the nanostructure. When the metal size is smaller than the wavelength of incident light and larger than the average electron-free path, a better enhancement effect can be obtained.\[^{25}\]

Fleischmann, et al.\[^{26}\] first obtained high-quality Raman spectral signals of monolayer-layer pyridine molecules modified on a rough Ag electrode surface, and thus discovered the SERS effect. The signal generated by this method was 106-fold stronger than that in pyridine solution. Subsequently, the phenomenon of millions of times of enhancement was systematically calculated as well as explained, and the corresponding spectrum generated by this phenomenon was called as surface-enhanced Raman spectroscopy.\[^{27,28}\] Due to the continuous development of nanomaterials, in 1997, a SERS experiment on single molecule on silver nanometer proved that SERS could be used to detect single molecule, and the strength of Raman scattering signal could be comparable to that of fluorescence signal, reaching an enhancement of about 14 orders of magnitude. The results provided a strong foundation for the future development and application of SERS.\[^{29,30}\]

**Advantages and challenges of SERS**

The application of SERS for heavy metals detection in food remains a challenge because the substrates require for ultrahigh sensitivity, excellent stability, convenient sampling and rapid response time.\[^{31,32}\]

Tip-Enhanced Raman Spectroscopy (TERS) enables precise manipulation of a nanometric substrate for highly sensitive SERS analysis.\[^{33}\] Aiming at improving the sensitivity, Li, et al.\[^{34}\] assembled Au@Ag nanorods and Ag nanospheres with opposite surface charge layer-by-layer on the tip of hollow optical fibers via electrostatic interaction. The synthesized three-dimensional (3D) structure had

---

**Figure 2.** Working principle of SERS: (a) schematic diagram of the targets on the surface of SERS substrates under light excitation, (b) illustration of the localized surface plasmon resonance effect, and (c) finite-element simulations of SERS enhancement distribution in single and coupled Au nanostructures.\[^{18}\]
a close gap inside, generating more hot spots between the nanorods and nanospheres, which dramatically elevated the SERS activity of the probe in the resultant 3D structure. The in situ cleaned 3D SERS substrates offered a rather suitable choice for SERS application in food quality monitoring.\cite{35} A highly sensitive and homogeneous 3D SERS substrate was synthesized using in situ ultraviolet ozone cleaning coupled with layer-by-layer self-assembly. Combining both advantages of two strategies, the SERS performance was further explored via setting and altering cleaning time. Under the optimal cleaning conditions, this strategy can provide clean and optimal surfaces for Raman detection, so as to obtain efficient plasmonic membranes populated with relatively uniform hot-spots. Furthermore, based on the optimal monolayer film, SERS property originated in plasmon coupling in multilayers structure of Au@Ag nanocubes substrates was systemically studied. The result showed that the 3D SERS enhanced effect was superior to the traditional two-dimensional (2D) SERS enhancement because the plasma coupling between layers (outside the surface) contributed a lot to the SERS light intensity. Meanwhile, the substrates also showed an excellent uniformity and good time stability.

To obtain an effective SERS probe, which uniformly distributed hot spots on wafer-scale substrates, Lee, et al.\cite{36} established a physical nanoimprint lithography method coupled with chemical deposition to fabricate a silver microbead array. Nanoimprint lithography can implement large-scale production and high flux, but cannot produce powerful hot-spots. However, the reaction time can reach 45 s and uniformly hot spots were formed in the gaps of the microbeads when electrochemical deposition was carried out on a nanoimprint lithography substrate. It conducted to improving the enhancement factor (EF) to $4.40 \times 10^6$ M with the low detection limit ($1.0 \times 10^{-11}$ M). Furthermore, a good substrate-to-substrate reproducibility (RSD < 9.4%) was also obtained. These researches open a new window for expanding the SERS application.

Additionally, many studies have employed flexible materials such as plastic, paper or polymer as convenience and low cost support surface to assemble more orderly plasmonic structures.\cite{37–39} PDMS is a kind of superhydrophobic plasma, compared with other plasmonic-based sensors, the comprehensive characteristics of solute concentration enrichment, the fourth power local electric field enhancement and increased light scattering can be concentrated on its rough surface. George, et al.\cite{40} fabricated flexible SERS substrates via replicating laser-written patterns created on PMMA for in situ reduction of the silver nanoparticles on the PDMS surface. The detection limit of rhodamine 6 G on their manufactured surface under resonance excitation at 532 nm is 8 nanograms and the EF of methyl orange was similar to $10^{10}$. Most remarkably, the replicated patterns displayed the lotus effect, and the silver nanoparticles possess superhydrophobic effect with high contact angle hysteresis.

Despite these successful experimental strategies, the synthesis of SERS platforms based on synthetic polymers and plastics is gradually becoming an issue viewing from the angle of sustainable development, as it takes many years for the used/discarded sensor to fully degrade in the environment. To address the problem, Ma, et al.\cite{41} exploited a biodegradable and environmentally friendly SERS platform on the basis of the previously fabricated gold-coated corn zein membrane coupled with an inverted pyramid structure of Au, Ag and Au@Ag nanoparticles deposition. When rhodamine 6 G was presented as SERS active molecule. The new hot spots were created by close proximity and contact between the Au surface and the newly added nanoparticles, leading to a highest EF up to $3 \times 10^5$. This sensitivity improvement not only enabled zein-based biodegradable SERS biosensor platform closer to non-biodegradable sensors, but also created a novel greener alternative.

In summary, SERS has shown far reaching application potential in the screening and detection of heavy metals in food and agro-products, which is worthy of more in-depth and comprehensive research.

**SERS in heavy metal detection**

As illustrated above, SERS is currently expected to become a powerful technique for heavy metals detection in food. The applications of SERS in heavy metal detection (Table 1), including mercury, arsenic, cadmium, lead, chromium and were discussed in detail, respectively.
<table>
<thead>
<tr>
<th>Metals</th>
<th>SERS Probes</th>
<th>Matrixes</th>
<th>LODs</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hg^{2+}</td>
<td>Facile silver film (Ag-film) coupled with a DNA molecular switch</td>
<td>The blood of a healthy person</td>
<td>$1.35 \times 10^{-6}$ pM</td>
<td>[42]</td>
</tr>
<tr>
<td></td>
<td>The stable sandwich structure (MB-TS-hDNA/AuNP-sDNA)</td>
<td>Spiked environment water samples</td>
<td>0.08 pM</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>AuNRs@Thymine</td>
<td>Untreated river samples harvested from Pearl River</td>
<td>1 ppb</td>
<td>[44]</td>
</tr>
<tr>
<td></td>
<td>Au@gap@AuAg Nanorod Side-by-Side Assemblies</td>
<td>Tissues and eggs of hens fed high-mercury diets</td>
<td>1 ppt</td>
<td>[45]</td>
</tr>
<tr>
<td></td>
<td>A gold nanospheres (Au NSs)-enhanced photoacoustic (PA) system</td>
<td>Water (Standard addition method)</td>
<td>78 pM</td>
<td>[46]</td>
</tr>
<tr>
<td></td>
<td>Aptamer-modified Au@Ag core-shell nanoparticles (Au@Ag NPs)</td>
<td>River water (collected from Xiangjiang River, China), tap water, and milk</td>
<td>0.4 pM</td>
<td>[25]</td>
</tr>
<tr>
<td></td>
<td>Histidine (H) conjugated perylene diimide (PDI) bolaamphiphile (HPH) as a dual-responsive optical marker</td>
<td>Drinking water</td>
<td>60 aM</td>
<td>[47]</td>
</tr>
<tr>
<td>Ag nanostructures along the microfluidic channel</td>
<td>Water (Standard addition method)</td>
<td>0.1 μM</td>
<td>[48]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rhodamine-stabilized gold nanobipyramids (Au NBs.)</td>
<td>Tap water and lakewater</td>
<td>0.5 pM</td>
<td>[49]</td>
</tr>
<tr>
<td></td>
<td>Gold nanoenzyme catalysis on the HAuCl₄·H₂O₂ to form gold nanoparticles (AuNPs)</td>
<td>Tap, river, and pond water (collected from Guangxi Normal University)</td>
<td>0.003 mol/L</td>
<td>[50]</td>
</tr>
<tr>
<td></td>
<td>Label-free Fe₂O₃@Ag</td>
<td>Drinking water and wastewater</td>
<td>10 pM</td>
<td>[51]</td>
</tr>
<tr>
<td></td>
<td>A magnetic Fe₂O₃@Ag nanomaterial</td>
<td>Water (Standard addition method)</td>
<td>0.1 pM</td>
<td>[52]</td>
</tr>
<tr>
<td></td>
<td>Di-(2-picolyl)amine (DPA) on gold nanoparticles (AuNPs)</td>
<td>Water (Standard addition method)</td>
<td>10 μM</td>
<td>[53]</td>
</tr>
<tr>
<td>As^{3+}</td>
<td>L-leucine as bio-recognition element based on graphene oxide (GO)</td>
<td>Waste water</td>
<td>0.5 ppm</td>
<td>[54]</td>
</tr>
<tr>
<td>And As^{5+}</td>
<td>Au@Ag core-shell nanoparticles</td>
<td>Lake water (from the East Lake of Wuhan, Hubei Province, China)</td>
<td>0.1 ppb</td>
<td>[55]</td>
</tr>
<tr>
<td></td>
<td>Fe₃O₄(core)-Au(shell) nanocomposite (DTT-Fe₃O₄@Au)</td>
<td>Tap water</td>
<td>0.86 ppb</td>
<td>[56]</td>
</tr>
<tr>
<td>Cd^{2+}</td>
<td>Alizarin functionalized on plasmonic gold nanoparticle</td>
<td>Drinking water</td>
<td>10 ppt</td>
<td>[57]</td>
</tr>
<tr>
<td></td>
<td>Gold nano-particles modified with trimercaptotriazine</td>
<td>Rice</td>
<td>8 μg kg⁻¹</td>
<td>[58]</td>
</tr>
<tr>
<td></td>
<td>A layer-by-layer self-assembly strategy by modification with an ion chelating reagent, 4-(4-phenylmethanethiol)-2,2'-6',2''-terpyridine (pmttp)</td>
<td>Water (Standard addition method)</td>
<td>20 μM</td>
<td>[59]</td>
</tr>
<tr>
<td>Pb^{2+}</td>
<td>GO based-up conversion nhms</td>
<td>Water (Standard addition method)</td>
<td>1.16 ppt</td>
<td>[60]</td>
</tr>
<tr>
<td></td>
<td>Saminobenzo-18-crown-6 (AB18C6) as a selective recognition molecule</td>
<td>Drinking water</td>
<td>0.69 pm</td>
<td>[61]</td>
</tr>
<tr>
<td></td>
<td>Graphene oxide nanoribbons</td>
<td>Water (Standard addition method)</td>
<td>0.7 nM</td>
<td>[62]</td>
</tr>
<tr>
<td></td>
<td>The Ag-doped carbon dots (CDAg)</td>
<td>Mineral water, tap water, wastewater of Bokanglou Laboratory of Guangxi Normal University and the pond water of Yanshan Campus of Guangxi Normal University</td>
<td>3.2 nM</td>
<td>[63]</td>
</tr>
<tr>
<td>Cr^{6+}</td>
<td>Alizarin red-sensitized colloidal TiO₂ nanoparticles (NPs)</td>
<td>Drinking water</td>
<td>0.6 μM</td>
<td>[64]</td>
</tr>
<tr>
<td></td>
<td>Hollow sea urchin-like TiO₂@Ag nanoparticles(NPs)</td>
<td>Water (Standard addition method)</td>
<td>1.45 nM</td>
<td>[65]</td>
</tr>
<tr>
<td></td>
<td>Amultifunctional satellite Fe₂O₃-Au@TiO₂ nano-structure</td>
<td>Chromite ore processing residue (COPR) and Cr(VI)-containing industrial wastewater</td>
<td>0.05 μM</td>
<td>[66]</td>
</tr>
<tr>
<td></td>
<td>Silver nanoparticles and lateral flow immunoassays (LFIAs)</td>
<td>Water (Standard addition method)</td>
<td>0.1 ppb</td>
<td>[67]</td>
</tr>
<tr>
<td></td>
<td>SA-protected AgNPs</td>
<td>Water (Standard addition method)</td>
<td>1.01 nM</td>
<td>[65]</td>
</tr>
<tr>
<td>Zn^{2+}</td>
<td>The di-2-picolylamine (DPA)-conjugated triaryl methane (TAM) dye</td>
<td>Water (Standard addition method)</td>
<td>50 μM</td>
<td>[68]</td>
</tr>
<tr>
<td>Cu^{2+}</td>
<td>Dipicolylamine-based ligand anchored onto plasmonic gold nanoparticles through the sulfur atom of the methylthio group</td>
<td>White wine</td>
<td>7.87 μM</td>
<td>[69]</td>
</tr>
<tr>
<td>F⁻</td>
<td>Combined diketopyrrolopyrrole with 1-butyl iodide</td>
<td>Water (Standard addition method)</td>
<td>0.7 nM</td>
<td>[70]</td>
</tr>
</tbody>
</table>
**SERS in mercury detection**

Mercury is one of the worst and most common contaminants of heavy metals in food. Exposure to Hg$^{2+}$, even in fairly small amounts, may trigger irreversible impairments to the central nervous system, resulting in degeneration and deterioration symptoms such as tremors, deafness, inability of coordination as well as sensation, or memory loss. Increase of the mercury levels were also related to negative effects on the reproductive and endocrine systems in both male and female. In light of these facts, the US Environmental Protection Agency (USEPA) has specify the maximum concentrations of Hg at 10 nM (2.0 ppb) in drinking water.

After the addition of Hg$^{2+}$, the signals of SERS probe would be attached to the single-stranded DNA, and then be significantly elevated as per the specific structural change in the DNA strands. The specific DNA molecular switch could be attached to facile silver film (Ag-film), to induce high identification as well as detection of Hg$^{2+}$. The magnetic-plasma resonance nanoparticles, which possess both magnetic and plasma resonance properties, can be used for SERS detection of Hg$^{2+}$ ions with super sensitivity. Based on “turn-off” mechanism, Zuo, et al. synthesized a magnetic Fe$_3$O$_4$@Ag nanomaterial for detecting Hg$^{2+}$ by SERS technology. The detection mechanism is based on competitive-binding interaction of Hg$^{2+}$ ions and malachite green with nanocrystals on Fe$_3$O$_4$@Ag magnetic beads. Without Hg$^{2+}$, the SERS signal intensity of malachite green is dramatically elevated by silver nanoparticles after malachite green was adsorbed to the Ag nanoparticles surface by a nitrogen atom. When Hg$^{2+}$ was added to the system, Ag/Hg amalgam was formed on the Fe$_3$O$_4$ @Ag surface due to the redox reaction occurring between zero-valent Ag nanoparticles and Hg$^{2+}$, which prevented the adsorption of malachite green on the silver nanoparticles surface. Therefore, Raman signal intensity of malachite green decreased proportionally as the concentration of Hg$^{2+}$ increases. Under optimized conditions, this label-free nano-sensor was highly selective as well as displayed an Hg$^{2+}$ detection amount of 10 pM.

Zhang, et al. isolated a stable sandwich structure via introducing magnetic field in the amplification process. In such a way, Hg$^{2+}$ can be sensitively identified and measured after multiple signal amplification. Yang, et al. proposed a SERS method with excellent sensitivity and selectivity for detecting Hg$^{2+}$ with a thymine sensor in place of the commonly used DNA. On this basis, the fundamental mechanism of the thymine SERS sensor was also studied more deeply, which made it possible to detecting other metal ions by means of replacing the metal ion-specific ligands. Yuan, et al. developed a Raman biosensor for ultrasensitive detecting Hg$^{2+}$ assembled by the Au@gap@AuAg side-by-side nanorods with powerful EM coupling. Remarkably, this synthesized biosensor was exploited to measure the total residual mercury amounts in the eggs and tissues of hens fed on high-Hg diets, respectively. The results indicated that the total mercury content of the collected yolks was about 20-fold higher than that of egg whites. This may be on account of a higher Hg binding capacity to proteins or amino acid in egg yolks than that in whites, and likely the large amounts of mercapto amino acid or proteins and methylase enzyme content in the egg whites, contributed to the conversion of more inorganic Hg into organic Hg. Photoacoustic method was also exploited for Hg$^{2+}$ detection with 4-mercaptophenylboronic acid (MPBA) as the aggregation agent. This method showed outstanding selectivity for Hg$^{2+}$ that was superior to the vulnerability to the other heavy metal ions. The system is cost-effective and possess an enormous potential for rapid detection of Hg$^{2+}$ trace amounts in water.

The metal nanoparticles have the nature of random dispersion, so it is tough to obtain stable, uniform and replicable SERS probes. There are two ways to solve these problems: the first is to combine SERS with other technologies to obtain a complementary detection system. Wu, et al. designed a ratio SERS adaptor sensor, which used the Au@Ag core-shell nanostructures when modifying the specific sequence of aptamer as the sensor probe, allowing the super-sensitive detection of Hg$^{2+}$. Furthermore, researchers have also developed a variety of dual-mode sensing methods such as colorimetry/SERS and SERS/fluorescence, all of which showed high selectivity and sensitivity to Hg$^{2+}$. The second solution is to integrate SERS detection into the micro flow control
platform. Yan et al. proposed a one-step chemical substitution reaction to synthesize silver nanostructures in microfluidic channels. The reaction can be done in 10 minutes compared with the few hours of the conventional methods. The microfluidic channel has a copper base and the silver ions can be reduced to silver nanoparticles in nitric acid solution. The SERS sensor assisted by microfluidics was used to detect Hg$^{2+}$ in aqueous solution, with good sensitivity and super selectivity. The prepared SERS active materials could be coupled with the concentration gradient generator to achieve continuous SERS detection. This simple technology can be used in any laboratory without requiring any bulky equipment, and can be integrated with other microfluidic networks for a large number of on-chip laboratory applications.

Furthermore, the analysis based on microfluidic paper can represent the promise of low-cost, flexible, original and portable analysis instrument. They typically consist of a small, patterned sheet of paper with a two-dimensional or three-dimensional structure, capable of testing dozens of microliters of liquid samples in a relatively short time, as supported by recent publications. However, the combination of SERS and microfluidic technology is still a big challenge at present, requiring multidisciplinary expertise and further research.

**SERS in arsenic detection**

The three main sources of arsenic pollution through the world can be categorized into natural groundwater, industrial effluent, and food and/or beverage contamination. People living in As-polluted areas often undergo serious health problems. Arsenic is a strong carcinogen in both acute and chronic ingestion, the dose and time as well as the oxidation state of As exposure are play decisive roles. Acute exposure to high amounts of inorganic as by individuals may be fatal. Long-term ingestion of small amounts of inorganic arsenic may trigger skin damage, peripheral nervous system disorders, anemia and leukopenia, liver disease, circulatory disease and cancer.

The signal intensity of 4-MBA can correspond to various amounts of As$^{3+}$. As$^{3+}$ added into uniform labeled Au@Ag bound to specific sequence of As$^{3+}$ aptamer, triggering the aptamer to be transposed from the Au@Ag surface and then resulting in aggregation of Au@Ag. As a result, the signal of 4-MBA was elevated because of the generation of hot spots. After diverse concentrations of As$^{3+}$ were added, the corresponding amount of As$^{3+}$ aptamer would displace from the surface of Au@Ag, and also led to corresponding aggregation process of Au@Ag. Utilizing the coffee ring effect on the separation potential of negatively charged AgNFs, four species of arsenic, namely As$^{3+}$, As$^{5+}$, MMA(V), as well as DMA(v), were identified and determined for fingerprint SERS signals in the solution and on the films, respectively. The formation of both concentric rings promoted the separation of arsenicals under the combined interaction of arsenicals with AgNFs, solvent, and surfactant. Combined the Raman signals and physical separation of arsenicals on the surface, arsenic speciation was realized by SERS technology based on AgNFs substrate, indicating the possibility of the coffee ring effect for rapid determination of small molecules using SERS.

L-leucine based on graphene oxide (GO) were exploited as bio-recognition element for the detection of arsenic. Remarkably, the real sample analysis results proved close agreement with those procured from standard techniques.

Xu et al. fabricated a 3D SERS probe, which was composed of silver or gold nanoparticles coated on electrospun PCL fibers, conducted a quantitative analysis on three different arsenic species: pAsA, Rox, and As$^{5+}$ with reliable detection level below 5 ppb. As$^{5+}$ detection in an ordinary solution of salt ions was confirmed, demonstrating the probe’s tolerance to more complex systems. The pAsA adsorption property on probe surface was systematically studied with the aid of the newly fabricated SERS substrates. In addition, the SERS spectral data were supported by DFT calculation. The effect of a dual-function nanocomposite on As$^{3+}$ in groundwater as an optical detection was investigated. the Fe$_3$O$_4$-Au nanocomposite was synthesized upon proper sulfuration reaction dithiothreitol. It can identify As$^{3+}$ in aqueous solution with ultra-low detection level and possesses great possible for rapid removal of As$^{3+}$ in water due to the presence of its magnetic core.
SERS in cadmium detection

Cadmium is a highly toxic contaminant with foodstuff being the main source of absorption by the general public.\(^8\) In accordance with the Chinese Centers for Disease Control and Prevention (CDC), cadmium ranks seventh among 275 harmful substances in the environment. The terminal half-life of Cd\(^{2+}\) in human organs is about 10–30 years, which implies that large number of Cd\(^{2+}\) may be bio-accumulated gradually along the food chain, even at ultralow doses daily.\(^{58}\) While the mean intake of Cd in European adults consumes 2.5 mg/kg per week. Cadmium exposure seriously damages the lungs, kidneys, liver and other organs initially by destroying intestinal flora, inducing inflammation of the gut and cell damage.\(^8\)

Alizarin functionalized on gold nanoparticle exhibited powerful SERS effect from the different Raman modes, which is suitable for heavy metal sensing detection in various ways. Dasary, et al.\(^57\) functionalized Alizarin as a Raman reporter on plasmonic gold surface, and then immobilized 3-mercaptopropionic acid and 2,6-Pyridinedicarboxylic acid at pH 8.5 on the nanoparticle surface for selective coordination of Cd\(^{2+}\). In the presence of Cadmium, the AuNRs displayed outstanding hotspot for Alizarin dye as well as SERS signal amplification. The fabricated plasmonic SERS assay was very sensitive for Cadmium sensing in drinking water samples.

The gold nanoparticles modified with trimercaptopriazine were applied as a ratio metric SERS probe, which enables quantitative sensing of Cd\(^{2+}\) in rice.\(^58\) The SERS signal was further elevated by utilized a conical holed substrate, followed by improving the sensitivity. A calibration model derived from the quantitative theory of spectral shape deformation was developed to reduce the influence of amount and distribution of “hot spots”. By this SERS substrate, the limit of detection in the actual sample of rice was about to be 8 \(\mu\)g·kg\(^{-1}\).

For detecting heavy metals in solution, the Raman probe was exploited by layer-by-layer self-assembly and then modified with an iron chelating reagent, named 4-(4-phenylmethanethiol)-2,2’:6’,2 “-terpyridine (PMTTP). Upon binding with metal ions, the metal ions in solution were identified and detected by the changes of Raman spectra. Cd\(^{2+}\) in aqueous solution was selected as an experimental sample. Similar to the determination of standard pH value, a rapid semiquantitative analysis of Cd\(^{2+}\) was achieved by simple calibration of a single point known standard solution.\(^59\)

SERS in lead detection

Lead is continually increasing owing to the needs of modern industrial, the World Health Organization (WHO) stated that “there is no known level of lead exposure that is considered safe”. Actually, trace amounts of lead in human blood may give certain probability of triggering high blood pressure, cardiovascular disease. Lead was associated with neurodevelopmental damage in children at even relatively lowest blood concentrations, these effects are likely to persist throughout the entire lifespan resulting in declined school performance, increased risk of substance abuse and incarceration, and declined economic productivity.\(^8\)

Aptamer (Apt) is an artificially selected short DNA/RNA chain that screened by SELEX in vitro,\(^87\) can specifically bind to different ligands, such as micromolecular, organic molecule as well as metal ions, etc. As a molecular recognition probe, it can provide an efficient and fast molecular recognition strategy for life science and analytical chemistry owing to the characteristics of its super selectivity, good affinity, easy labeling, long-term stability, and convenient synthesis. In many previous studies, various well-known specific aptamers with the good ability to form G-quadruplex structure have been introduced into Pb\(^{2+}\) recognition.\(^63,88\)

GO nanoribbons have a powerful catalytic effect on the formation of gold nanoparticles by \(\text{H}_2\text{O}_2\), reduction of HAuCl\(_4\), and the gold nanoparticles displays nano plasmonic SERS activity, Rayleigh scattering and absorption. If an aptamer against Pb\(^{2+}\) is exist in solution, it will bind to GO nanoribbons and thus inhibits their catalytic activity. After Pb\(^{2+}\) was added, it will combine with the
Apt to form stable complexes and releases free GO nanoribbon. These cause the SERS intensity at 1615 cm\(^{-1}\) to amplified when the molecular probe Victoria Blue B existed.\[^{62}\]

Wang, et al.\[^{63}\] exploited novel carbon dots doping with Ca, Ag and Au and analyzed their catalytic properties. The Ag-doped carbon dots (CDAg) acted as mimic enzyme in the HAuCl\(_4\)·H\(_2\)O\(_2\) reaction was found to generate nanogold particles with SERS and RRS effects. the CDAg surface adsorbed the Apt, weakening the catalysis. The addition of Pb\(^{2+}\) would combine with the Apt to form strong complexes Pb-Apt and desorb CDAg which restored its catalytic effect.

NHMs have been widely used in various industries, especially in the field of sensors. Among NHMs, the conversion of NHMs system based on GO is a growing field for quick detecting various hazardous substances as a sensor technology based on aptamer or free-labeled.\[^{60}\] In order to accurately detect Pb\(^{2+}\) in water, NaYF\(_4\)@Yb, Ho and Au NHMs system was fabricated, respectively.

**SERS in chromium detection**

Cr has been added in quantity in many industrial processes and has become a main environmental hazards.\[^{89}\] it enters the body’s digestive tract through breathing, food or skin contact.\[^{90}\] The harm degree of metal Cr of different valence state to human body is different, Cr\(^{5+}\) has around 1000 times more pernicious than Cr\(^{3+}\), that is due to its oxidizing power.\[^{91}\] The effects of the metal in two different states have greatly discrepant impact on human, a proper level of Cr\(^{3+}\) is reasonably nontoxic and is even regarded as an essential in mammals for the metabolism of glucose, fat, and protein. On the contrary, Cr\(^{5+}\) is carcinogenic and mutagenic.

A dye-sensitized semiconductor system in combination with semiconductor-enhanced Raman spectroscopy was used to metal ions detection, on the basis of “turn-off” SERS method that fully utilizing the intrinsic capacity of the semiconductor to catalyze the degradation of the SERS probe. Taking alizarin red-sensitized colloidal TiO\(_2\) nanoparticles as a typical sample, \[^{61}\] et al.\[^{64}\] illustrated how the determination of Cr\(^{5+}\) in water can be realized by semiconductor enhanced Raman spectroscopy.

Bu, et al.\[^{65}\] developed the hollow sea urchin-like TiO\(_2\)@Ag nanoparticles for highly sensitive identification and detection of Cr\(^{6+}\) by SERS. The TiO\(_2\)@Ag NPs was specifically functionalized by glutathione (GSH) and employed as substrates with 2-MPy as a Raman reporter for a recyclable SERS-active sensor. Its excellent selectivity to Cr\(^{6+}\) is obviously higher than that of other metal ions, and promising application for quantitatively detecting Cr\(^{6+}\) in water. Using citrate-capped gold nanoparticles, Ye, et al.\[^{92}\] demonstrated an outstanding SERS probe for detecting trivalent Cr\(^{3+}\). Upon introducing Tween 20 into citrate-capped gold nanoparticles solution, this fabricated Tween 20/citrate–AuNP probe was able to identify Cr\(^{3+}\) at an ultra-low amount (50 nM) in the aqueous medium with a pH of 6.0. Tween 20 can stabilize AuNPs with citrate coating under high ionic strength and AuNPs aggregated because of the chelation between Cr\(^{3+}\) and citrate ions. Thereby it formed a few hot spots as well as realized a great amplification of the Raman intensity via EM field enhancements. Specific mechanism for enormous Raman intensity variation were studied. this system showed that a great selectivity for Cr\(^{3+}\) was 400 times, dramatically higher than other metal ions.

Lv, et al.\[^{66}\] synthesized a multifunctional satellite Fe\(_2\)O\(_4\)·Au@TiO\(_2\) nano-structure for detecting Cr\(^{6+}\) by SERS method. Both the results and 3D FDTD simulation illustrated that Fe\(_2\)O\(_4\)·Au surface was coated with 2–6 nm thick TiO\(_2\) layer to prevent direct contact and reaction between SERS substrates and Cr\(^{6+}\), and enabled Cr\(^{6+}\) to be enriched near the gold nanoparticles to further improving its SERS sensing. The selectivity of the substrate to Cr\(^{6+}\) was better than that of other co-existing ions, and accurate quantitative results were obtained in the complex environmental matrix. What’s more, the photocatalytic reduction reaction of Cr\(^{6+}\) with this multifunctional material was in line with first-order kinetics, and the on-site monitoring of the reduction process showed a good SERS effect with a reduction rate of almost 80%.

Lateral flow immunoassays (LFIAs) was widely used in the area of medicine, agriculture and food safety with the advantage of inexpensive, simple, hand-held and robust. Liang, et al.\[^{67}\] reported a convenient and highly sensitive SERS band sensor combined AgNPs and LFIAs. Due to the rapidity
and robustness of LFIAs and super sensitivity of SERS, the combination of the both showed quick, excellent property and may allow for the semiquantitative detection of Cr$^{3+}$, with the LOD decreased to $10 - 5\text{ngmL}^{-1}$, which is 105 times over than those previously employed within 15 minutes.

On the basis of redox reaction of carbimazole with target ions, a SERS strategy was implemented for detecting Cr$^{6+}$ in water using SA-protected AgNPs as substrates. After adding Cr$^{6+}$, the Raman signal intensity of carbimazole was inversely proportional to the amount of dichromate added and thus indirectly corresponds to the concentration of Cr$^{6+}$.[65]

**SERS in other heavy metals detection**

Besides these heavy metals mentioned above, some other heavy metals are also widely found in food contamination and detected as standard monitoring indicators (Fig. 3).

Intake of zinc(Zn) in excess by human body has been shown to affect the HDL levels and destroy the immune system.[68,94] Lee, et al. synthesized a novel SERS substrate of the DPA-TAM dye aiming to Zn$^{2+}$ ions detection. The enhanced SERS intensity of DPA-TAM on the gold nanoparticles was due to increase of Zn$^{2+}$ concentrations. Their probe showed that [Zn$^{2+}$]-associated SERS intensities was relatively low with a detection amount of 50 μM approximately, which depends on plasmonic amplification effect from the well-dispersed metal nanostructures to DPA-TAM-AuNP aggregates, which are activated by Zn$^{2+}$.

Copper (Cu) in moderate amounts is essential to the human diet but toxic when exist in excess and may lead to metabolic disorders, disturb the central nervous system, and trigger the immunotoxicity, anemia and growth poisonousness.[95,96] A molecular sensor based on SERS for analyze Cu$^{2+}$ ions with high specificity and good selectivity was realized by immobilizing a fabricated dipicolylamine-based ligand anchored on the surface of AuNPs via the sulfur atom of the methylthio group. What’s more, this fabricated molecular sensor was implemented for detecting Cu$^{2+}$ in white wine, showing that novel SERS-based molecular sensor was promising as a routine method to control the Cu$^{2+}$ level in wine.[69]

Excessive intake of fluoride ions can lead to oxidative stress, regulate intracellular redox homeostasis, and trigger mitochondrial damage, endoplasmic reticulum stress and alter gene expression. Therefore, the detection and quantification of its residues in food are of great significance. Using the catalytic enhancing strategy and the TMBOX molecular probes, SERS and fluorescence method can be considered for the detection of ultra-trace F$^-$. Li, et al.[97] synthesize a SERS probe in combination of diketopyrrolopyrrole and 1-butyl iodide that was induced by F$^-$ to amplify SERS signal, and the SERS detection for F$^-$ was improved to $1.0 \times 10^{-3} - 1.0 \times 10^{-6}$ mol/L. The stable complex, [FeF$_6$]$^{3+}$, generated after fluoride ion (F$^-$) were added, and could inhibit the catalytic effect of Fe$^{3+}$, leading to a positive proportional reduction of both the signal of SERS and fluorescence and the TMBOX concentration.[70]

**Chemometrics and multivariate analysis**

**Chemometrics as data analysis technique in SERS**

Reliable quantitative and qualitative analysis of original SERS spectra is a vital process to promote the extremely precise development of the technique.[31,98] As with most spectroscopic techniques, Raman requires advanced data processing to extract effective information from spectra.[99,100] Except the information about these target molecules, it can display other details about the target detectors as well by the affected photons, including size, color and temperature, which result in variation of spectral absorbance, wavelength and drift.[101] Therefore, chemometrics can be employed to pretreat the original spectrum, dig out the major information, eliminate drift in the background as well as efficiently compress the data.[102,103] By removing singular values that in the model which affects predicted results and selecting spectral variables associated with the research, the property of
Figure 3. Schematic illustration of SERS sensors for heavy metals detection. (A) Mechanism of the SERS sensor for the detection of mercury ions (Hg$^{2+}$), based on the T-Hg$^{2+}$-T coordination.\(^{42}\) (B) Scheme of SERS detection of trace F$^-$ and Fe$^{3+}$ with TMBOX molecular probes in Ag nanosol substrate based on the catalytic oxidation of TMB.\(^{70}\) (C) Fabrication of hollow sea urchin-like TiO$_2$ @Ag NPs for Cr$^{6+}$ detection.\(^{93}\) (D) Schematic illustration of the formation of a partition layer on the surface of the Au NBs and the dual-modal sensing of Hg$^{2+}$\(^{49}\).
prediction by the model can be increased effectively. This will contribute to build a more accurate multiple calibration model.\cite{104,105}

Many supervised learning algorithms have been employed to analyze Raman spectra, which can be separated into distinct sub methods: (1) methods based on discriminant analysis, for example partial least-squares followed by a discriminant analysis (PLS-DA) or discriminant function analysis (DFA); (2) artificial neural network (ANN) based models, for example the multilayer perceptron (MLP) or support vector machine (SVM); (3) models based on regression analysis such as principal components regression (PCR), or partial least squares (PLS); (4) models on the basis of regression trees like random forests (RF), and classification and regression trees (CART); and finally (5) evolutionary-based algorithms like genetic algorithm (GA) and computing (respectively GP and GC), evolutionary algorithm (EA), and evolutionary programming (EP).\cite{99} Although there have been many applications of Raman combined data processing algorithm, it still needs many explorations to apply various data processing methods in heavy metal detection.

**Application of chemometrics in SERS detection of food**

As a baseline emendation method, adaptive iteratively reweighted penalized least squares (air-PLS) can adaptively and iteratively adjust the weight of squares sum of residual difference between the fitting baseline and the original signal, so as to calculate and deduce the irregular baseline rapidly and flexibly, and enable the smooth denoising of the signal. Moving windows partial least squares (MWPLS) algorithm can move windows via the whole band region and acquire the evaluation parameters of each window.\cite{105} In order to reduce the interference of baseline drift on the original SERS spectrum, standard normal variance (SNV) was implemented. SNV processes each spectrum to reduce the influence of scattering and solve the problem of overlapping peaks.\cite{104} Air-PLS strategy was employed to subtract matrix background and decrease baseline spectral drift and MWPLS strategy was introduced to pick the optimal wavelength combination as well as establish a concentration prediction model with a correlation coefficient above 0.99.\cite{105} The processed spectra were imported into MATLAB R2017a and PLS algorithm was used for baseline correction, followed by utilizing the smoothing parameter of 10,000 coupled with the asymmetry parameter of 0.001.\cite{106}

Chen, et al.\cite{107} reliably predicted the concentration of phosphorus in methanol aqueous solution and oolong tea samples by establishing PLS regression model. Ahmad, et al.\cite{108} assembled liquid microextraction, SERS as well as chemometric algorithms in a platform for Cr\textsuperscript{6+} speciation employing octahedral Cu\textsubscript{2}O@Ag nanocomposites (Cu\textsubscript{2}O@AgNCs) as a Raman probe. PLS as well as variable selection competitive adaptive reweighted sampling (CARS)-PLS were employed for masking redundancy in Raman spectra of the complex ion binding (RG (+) center dot CrO\textsubscript{3}Cl\textsuperscript{-}) fabricated in sediment phase extraction. Furthermore, using SERS combined with multivariate calibration methods, a fast, simple and sensitive strategy for detecting mercury ion residue in dairy products was established.\cite{109}

An environmentally safe SERS method was exploited for detecting trace amitraz in honey with silver nanoparticles array substrate, which synthesized by an oblique angle deposition method possessed an outstanding SERS activity. The characteristic peaks of amitraz peak are determined by DFT calculation. Specifically, PLS analysis was utilized to establish a multiple-quantitative predicting model of amitraz. Preliminary results displayed that the predicted concentrations of amitraz in honey differs little from their actual concentrations.\cite{110}

**Application of density functional theory (DFT) in SERS**

DFT is an increasingly appropriate strategy for modeling the properties of electronic structure of multi-electron systems.\cite{111} The Spectral detections of procaine at a trace level was successfully completed employing SERS platform and nano-silver substrates. Raman spectral intensities related
to \(-C = O\) stretching, \(-C-N\) stretching as well as \(-NH_2\) bending vibrations were significantly enhanced. The DFT calculation not only provided the basis of final allocation of SERS mode, but also clarified the interaction mechanism between Ag-Np and procaine at the micro-scope level.\[^{112}\]

Botta, et al.\[^{113}\] employed SERS method to classify the acids with silver nanorods arranged in zigzag pattern as active substrate. SERS and chemometric methods of principal component analysis were utilized to detect and classify volatile fatty acids (VFA). The Raman vibrations were understood by DFT calculations and compared with experimental observations to assist in the distribution of spectral line. Huff, et al.\[^{111}\] found the percentage of Hartree-Fock exchange used by DFT calculation varied linearly with the predicted excitation energy existed. This enables the hybrid functional to precisely predict the band gap of four different oligothiophenes. For example, a four-unit less thiophene absorbed at 379 nm (3.27 eV) requires 33% HF, while a ten-unit less thiophene absorbed at 458 nm (2.71 eV) requires 46%. Furthermore, the vibration of amikacin has been performed experimentally and theoretically. The molecules were characterized by Raman spectroscopy and infrared spectroscopy coupled with DFT calculation.\[^{114}\]

**Substrate assisted detection of heavy metals with SERS sensor**

A good substrate requires ultra-high sensitivity, excellent stability, convenient sampling and rapid response time.\[^{115,116}\] The disadvantages of commonly used rigid substrates, such as glass and silicon wafers, are high price, complex production process, and environmental pollution. Although flexible substrates overcome the above disadvantages, they can only be applied to solid surfaces, not to liquid or food internal detection. As the surface morphology of the base adsorbed by the molecules was an important factor affecting the occurrence of SERS effect and the strength of SERS signal,\[^{115}\] the bearing matrix of the molecules was crucial. Therefore, the research on SERS active bases has been one of the research hotspots in this field.

**The construction of micro-scale substrate platform**

Research on Raman enhanced ultra-sensitive detection has traditionally focused on SERS or TERS from primary Raman active materials (typically monolayers of Au and Ag nanoparticles). However, owing to a lot of inherent disadvantages, the applicability of these traditional methods was limited. Therefore, a third dimension was added to obtain a next generation of enhanced Raman sensing by employing the concept of molecular level detection with gaps in nanostructures (Fig. 4). Unlike conventional SERS or TERS platform, the platform at the atomic level also immune to excitation wavelengths and show great possibility for universal sensors. Furthermore, this portable platform provided novel ideas for lots of non-destructive, hypersensitive and several other sensing applications. The atom-scale platform possesses two followed characteristics: multi-tip probes encapsulates layers of voids at the atomic level, the mechanism of multi-photon ionization was carried out for the fabrication.\[^{117}\]

Nemciauska, et al.\[^{118}\] exploited a novel SERS method for molecular sensors with a combination of the hybrid nano-plasmonic silicon membrane and gas micropump. They improved the performances of interaction between the analytes and the plasmonic structures of SERS substrate by pumping contaminated gases or liquids into silicon membrane, which decorated with silicon-flowered nano-structures (“hot spots”). The theoretical calculation of the designed sensor was used to determine the optimal conditions for trace amounts of molecules and then the Raman scattering was amplified by flowing through and interacting with SERS substrate (“hot spots”). SolidWorks software was used to simulate the gas flow so as to the optimization of the sensor chip structure. 3D printing technology was also utilized in the experiment to designed, simulated and manufactured the structure of sensor chip. The nanomolar sensitivity of gas detection was realized by this platform and the types of analytes were identified reliably based on SERS spectral fingerprints.
The construction of macro-scale substrate platform

The superhydrophobic surface was considered to be an ideal alternative SERS substrate for precise detection because of its ability to concentrate highly diluted solutions. The superhydrophobic capabilities was coupled with plasmonic nanostructures seas SERS “hot spots” to exploited nanostructured superhydrophobic SERS substrates using femtosecond laser pulses directly on the surface of Cu without additional Au/Ag coating. In addition to making the surface display superhydrophobic capability to concentrate the target analyte, The Cu nanostructures also conducted to the field enhancement. The synergistic effects of copper nanostructures and silver nanoparticles showed an great improvement over those silver coating methods.\[119\]

He, et al.\[120\] exploited a microdroplet-captured tape for sensitive SERS screening of food contaminants. Figure 5 illustrates the overall manufacturing scheme and analysis points of this portable tape sensor. The main sensing unit was located on the microwave unit functionalized in the conductive carbon band, which was easy fabricated by physical punching, magnetron sputtering and electrochemical deposition of gold nano-dendrites. The tape-based sensors can be attached droplets to gloves by dipping them directly out of the original analytical solution. Through simple sampling, early-warning detection of contaminants such as sultan-1 and thiabendazole in actual food items could be also realized.

A unique optical behavior, occurred by the interaction between plasmonic nanoparticles and a dielectric platform, could further promote the plasmonic/SERS properties of the substrate. Ag@SiO2 nanotubes were assembled on Fe – TiO2 nanometer board modified paper, which could be employed to prepare dielectric modified plasma paper SERS substrate. The visible light response of Fe-TiO2 nanomaterials dramatically changes the paper’s optical properties and served as a dielectric substrate for the silver nanocrystals. The average EF of dielectric modified plasma paper prepared with R6G as probe molecule was $1.49 \times 10^7$. Compared with unmodified plasmonic paper, this value emphasized the coupling effect of the dielectric nanosheets and showed certain advantages.\[121\]
Conclusions

The detection of heavy metals in food and agro-products is an indispensable aspect to ensure food safety. In recent years, despite the rapid progress of the available techniques, the non-invasive simple and feasible criteria of SERS technology has provided a wider range of possibilities for faster and low-
cost detection of heavy metals in food. This review summarized the basic principle, advantages and limitations of SERS and its current applications in Hg$^{2+}$, As$^{3+}$, Cd$^{2+}$, Pb$^{2+}$, Cr$^{6+}$ detection from food. The review discussed the potential of combining chemometrics and multivariate analysis with SERS in order to unravel the novel SERS substrate platforms using both macro and micro scale. Future studies should focus on the formation of standardized testing protocol, development of novel green biodegradable substrate platform with low cost, combination of SERS technology and microfluidic platform, utilization of chemometrics and multivariate analysis for data processing to aid the optimum investment in SERS technology.

**Abbreviations**

2-MPy, 2-Mercaptopyridine; 4-MBA, 4-Mercaptobenzoic acid; AAS, Atomic absorption spectroscopy; air-PLS, Adaptive iteratively reweighted penalized least squares; ANN, Artificial neural network; ARS, Alizarin red; CART, Classification and regression trees; CDC, Centers for Disease Control and Prevention; DFA, Discriminant function analysis; DFT, Density functional theory; DMA(v), Dimethyl arsenic acid; DPA-TAM, Di-2-picolylamine- conjugated Triarylmethine; EA, Evolutionary algorithm; EF, Enhancement factor; EM, Electromagnetic; EP, Evolutionary programming; FDTD, Finite difference time domain; GA, Genetic algorithm; GC-MS, Gas chromatography-mass spectrometer; GO, Graphene oxide; GSH, Glutathione; HDL, High-density lipoproteins; HPLC, High performance liquid chromatography; ICP-MS, Inductively coupled plasma mass spectrometry; LC-MS, Liquid chromatography-mass spectrometer; LFIAs, Lateral flow immunoassays; LOD, Limit of detection; MLP, Multilayer perceptron; MMA(V), Monomethyl arsenic acid; MPBA, 4-mercaptophenylboronic acid; MWPLS, Moving windows partial least squares; NHMs, Nano hybrid materials; pAAs, P-Arsanilic acid; PCL, Polycaprolactone; PCR, Principal components regression; PDMS, Polydimethylsiloxane; PLS, Partial least squares; PLS-DA, Partial least-squares followed by a discriminant analysis; PLSR, Partial least square regression; PMMA, Polymethylmethacrylate; PMPTP4, (4-Phenylmethanethiol)-2,2′,6′,2′′-terpyridine; RF, Random forests; Rox, Roxarson; RRS, Rayleigh scattering; SELEX, Systematic evolution of ligands by exponential enrichment; SERS, Surface-enhanced Raman spectroscopy; SNV, Standard normal variance; SVM, Support vector machine; TDS, Total diet study; TERS, Tip-enhanced raman spectroscopy; THQ, Target hazard quotient; TMBOX, 3, 3′, 5, 5′-Tetramethylbenzidine diimine; USEPA, United states environmental protection agency; VFA, Volatile fatty acids; WHO, World Health Organization.

**Credit author statement**

Zhiming Guo: Conceptualization, Supervision, Funding acquisition, Project administration. Ping Chen and Nermeen Yosri: Writing - original draft. Quansheng Chen: Resources. Hesham R. El-Seedi, Xiaobo Zou and Hongshun Yang: Writing - review & editing. All authors read and approved the final manuscript.

**Declaration of competing interest**

The authors declare no conflict of interest.

**Acknowledgments**

The authors acknowledge the financial support provided by the National Natural Science Foundation of China (31972151), National Key R&D Program of China (2018YFC1604401), Key R&D Project of Jiangsu Province (BE2018307, BE2019359), China Scholarship Council (CSC) (201908320217), the Postgraduate Research and Practice Innovation Program of Jiangsu Province (SJCX20_1429), and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

**Funding**

This work was supported by the National Natural Science Foundation of China [31972151]; National Key R&D Program of China [2018YFC1604401]; Key R&D Project of Jiangsu Province [BE2018307, BE2019359]; China Scholarship Council (CSC) [201908320217]; the Postgraduate Research and Practice Innovation Program of Jiangsu Province [SJCX20_1429], and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).
References


