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REVIEW ARTICLE

Onsite/on-field analysis of pesticide and veterinary drug residues by a state-of-art technology: A review

Md. Musfiqur Rahman[1] | **Dong Ju Lee**[1] | **Ara Jo**[1] | **Seung Hee Yun**[1] | **Jong-Bang Eun**[2] | **Moo-Hyeog Im**[3] | **Jae-Han Shim**[1] | **A. M. Abd El-Aty**[4,5,*]

[1] Natural Products Chemistry Laboratory, Chonnam National University, Gwangju, Republic of Korea

[2] Department of Food Science and Technology and BK 21 plus Program, Graduate School of Chonnam National University, Gwangju, Republic of Korea

[3] Department of Food Engineering, Daegu University, Gyeongbuk, Republic of Korea

[4] Department of Pharmacology, Faculty of Veterinary Medicine, Cairo University, Giza, Egypt

[5] Department of Medical Pharmacology, Medical Faculty, Ataturk University, Erzurum, Turkey

Correspondence
J-H. Shim, Natural Products Chemistry Laboratory, Chonnam National University, Yongbong-ro 77, Buk-gu, Gwangju 500–757, Republic of Korea.
Email: jhshim@jnu.ac.kr

*Additional corresponding author: A. M. Abd El-Aty Email: abdelaty44@hotmail.com

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Pesticides and veterinary drugs are generally employed to control pests and insects in crop and livestock farming. However, remaining residues are considered potentially hazardous to human health and the environment. Therefore, regular monitoring is required for assessing and legislation of pesticides and veterinary drugs. Various approaches to determining residues in various agricultural and animal food products have been reported. Most analytical methods involve sample extraction, purification (cleanup), and detection. Traditional sample preparation is time-consuming labor-intensive, expensive, and requires a large amount of toxic organic solvent, along with high probability for the decomposition of a compound before the analysis. Thus, modern sample preparation techniques, such as the quick, easy, cheap, effective, rugged, and safe method, have been widely accepted in the scientific community for its versatile application; however, it still requires a laboratory setup for the extraction and purification processes, which also involves the utilization of a toxic solvent. Therefore, it is crucial to elucidate recent technologies that are simple, portable, green, quick, and cost-effective for onsite and infield residue detections. Several technologies, such as surface-enhanced Raman spectroscopy, quantum dots, biosensing, and miniaturized gas chromatography, are now available. Further, several onsite techniques, such as ion mobility–mass spectrometry, are now being upgraded; some of them, although unable to analyze field sample directly, can analyze a large number of compounds within very short time (such as time-of-flight and Orbitrap mass spectrometry). Thus, to stay updated with scientific advances and analyze organic contaminants effectively and safely, it is necessary to study all of the state-of-art technology.

KEYWORDS
biosensor, ion mobility, onsite analysis, quantum dot, residue detection, surface-enhanced Raman spectroscopy

Abbreviations: AChE, acetylcholinesterase; APT, aptamer; EC, Delectron capture detection; FID, flame ionization detection; FLD, fluorescence detection; FLISA, fluorescence linked immunosorbent assay; FPD, flame photometric detection; FRET, fluorescence resonance energy transfer; GO, graphene oxide; IFE, inner filter effect; IM–M, Sion mobility–mass spectrometry; MIP, molecularly imprinted polymer; N–CD, snitrogen-doped carbon dots; QD, squantum dots; SER, Ssurface-enhanced Raman spectroscopy; UVD, ultraviolet detection

1 | INTRODUCTION

The chemical contamination of food is a topic of concern that is mainly concerned with agrochemicals (pesticides and veterinary medicines) and environmental contaminants, such as persistent organic pollutants [1]. Various classes of compounds, including insecticides, herbicides, molluscicides, rodenticides, nematicides, and plant growth regulators, are termed pesticides. Organochlorines, organophosphates, carbamates, and pyrethroids are frequently utilized insecticides in agricultural commodities [2]. Conversely, antibiotics, antimicrobials, antihistamines, antiprotozoals, and hormones are classified as veterinary drugs [3]. Ideally, pesticides and veterinary drugs should be specifically fatal to the targeted microorganism, but harmless to non-targeted animals and humans [4]. However, indiscriminate application of pesticides and veterinary drugs leaves unwanted residues in foods and the environment [5,6]. Moreover, the excessive application of these chemicals under the assumption, "if little is good, a lot more will be better," has worsened the situation [7]. Therefore, the monitoring of pesticides and veterinary drug residues is mandatory to impose regulations and secure food safety.

Various techniques have been utilized to analyze/monitor pesticides and veterinary drugs. Gas chromatography (GC) combined with various traditional detection techniques (electron capture detection (ECD), flame photometric detection (FPD), flame ionization detection (FID), and liquid chromatography (LC) combined with ultraviolet (UVD) and fluorescence detection (FLD) techniques are the most frequently employed techniques for analyzing pesticide and veterinary drug residues in food and environmental samples [8–19]. However, extensive sample preparation is required to extract the target analytes before employing these traditional methods of detection. Further, traditional sample preparation requires liquid–liquid solvent extraction and purification via column chromatography (CC), which are time-consuming [20]. However, with the advancement of technology, mass spectrometry (MS), which can be easily assembled with GC or LC, has become a popular tool for analyzing pesticides and veterinary drugs with the required sensitivity. Therefore, LC–MS/MS and GC–MS/MS have become the common techniques in most residue analytical laboratories. Based on this sensitive technique, several facile sample preparation methods for analyzing pesticides and veterinary drugs have been developed [21–52]. Among them, the most popular and frequently employed method is the quick, easy, cheap, effective, rugged, and safe (QuEChERS) approach. QuEChERS extraction involves the extraction of 10/15 g of a sample by 10/15 mL of a solvent, followed by salting out with a novel magnesium sulfate and sodium chloride salt/sodium acetate/citrate buffer; the purification is performed mostly with primary–secondary amine (PSA) and a C18 octadecyl sorbent in a dispersive solid-phase extraction (d-SPE) procedure [53–55].

Although the LC–GC system coupled with mass spectrometry can analyze complex mixtures, the maintenance of these power-consuming, table-top instruments is relatively expensive. However, sample preparation is still a time-consuming and expensive procedure even with the utilization of modern technologies. Additionally, samples that are collected, transported to the laboratory, and preserved for analysis, sometimes obtain different outcomes from those of the actual ones because of the probability of degradation [56]. Therefore, the demand for onsite analysis of food and environmental samples increases daily because it reduces the risk of contamination, loss of analyte, and the probability of analyte degradation during transport. Moreover, onsite monitoring achieves results quickly. Therefore, handy devices requiring minimum maintenance are perfect instruments for onsite analyses [56]. Much effort has been invested in the on-field detections of pesticides and veterinary drugs in food and environmental samples. Surface-enhanced Raman spectroscopy (SERS), use of quantum dots (QDs), biosensing, miniaturized GC, and ion mobility–MS (IM–MS) are among the techniques for on-field detections. This study aims to review the state-of-the-art technology for the onsite analyses of pesticides and veterinary drugs in food and environmental samples.

2 | SURFACE-ENHANCED RAMAN SPECTROSCOPY AND ITS APPLICATION IN THE ANALYSES OF PESTICIDES AND VETERINARY DRUGS

Raman spectroscopy affords the structural fingerprint of molecules by determining the vibrational modes by which the molecules can be identified [57]. When monochromatic light interacts with molecules, most of the lights are scattered at the same energy of incident ray, i.e., when the light retains its energy, it is known as elastic scattering or Rayleigh scattering [58,59]. Conversely, when a small amount of the photons (~0.000001%) of this ray is scattered at a different frequency from that of the incident light, it is termed inelastic scattering or the Raman effect [60]. The principle of Raman spectroscopy is graphically shown in Supporting Information Figure S1.

It is very easy to acquire a Raman spectrum with minimum or zero sample preparation, thereby canceling the possibility of leaving any sample waste [61,62]. A transparent plastic, glass, solvent, or water is typically employed to acquire the Raman signal [62], [63]. However, owing to

weak, inelastic scattering, it was very challenging to separate the Raman signal from the intense elastic scattering. Therefore, the technique is not readily utilized for the long-term routine monitoring of food and environmental samples[64]. With the advancement of reproducible surfaces, Raman signals can now be enhanced by 10^4–10^{14} [64].

In 1974, Fleischmann et al. reported the SERS effect for the first time while working with Ag electrodes-adsorbed pyridine [65]. However, the findings were not confirmed until 1977 when Albrecht and Creighton (1977) and Jeanmaire and VanDuyne (1977) published separate studies on the enhancement of the Raman signal of the Ag-electrodes-adsorbed pyridine by 5–6 orders [66,67]. Further, several SERS substrates have been reported. Moreover, rough metal electrodes, noble metals, transition metals, and semiconductor nanomaterials and composites are notable substrates [68]. Among them, the rough metal substrate is the oldest. However, the uncontrollable electrode process, which did not allow its theoretical study, was the main drawback of this substrate. Therefore, Au and Ag nanoparticle-based substrates are popular owing to their low cost, simplicity, and suitable signal magnification [69,70]. With the continuous improvement of SERS for over 40 years, SERS-active materials have been redesigned from transition and noble metals into semiconductor materials with improved stability, photoluminescence, band gap, and resistance to degradation [71]. Recently, it was observed that semiconductors (TiO_2 and CdTe) could afford higher enhancement ($>10^6$) under optimized conditions [72,73]. Moreover, traditional SERS substrates have been transformed from rigid to flexible materials, such as cellulose paper, in which noble metal nanoparticles are decorated onto flexible frameworks to render the substrates inexpensive, flexible, and portable [74].

Following a similar trend, Ma et al. (2018) invented screen-printed paper-based SERS swabs for the onsite detection of pesticide residues. In their study, which employed a screen-printing technique, Ag nanoparticles and graphene oxide (GO) were successfully decorated on a cellulose paper (Ag NPs/GO paper). Thiram, thiabendazole, and methyl parathion were detected at 0.26, 28, and 7.4 ng/cm^2 levels, respectively [75].

Several studies have been conducted to apply the SERS technology to the detection of pesticides and veterinary drugs. Some of the representative analytes are listed in **Table 1**.

For the SERS measurements, a 785-nm laser (17 mW) was employed for the excitation, a QE65000 (Ocean Optics) portable spectrometer was employed for the detection, and a fiber optic probe (InPhotonics) was employed for the delivery of the laser light and the collection of the scattered photons. The wavelength, 785 nm, was selected because of the inexpensiveness and portability of 785-nm laser diodes, as well as the reduction that is gained in the background fluorescence by operating at long wavelengths [74].

For simple, sensitive, cheap, rapid, and onsite detection capability, SERS is the future technology of interest for pesticide and antibiotics analysis [111–113]. Furthermore, with the development of a mass spectral library and semiconductor–metal hybrid substrates, SERS would become a robust technology for analyzing the external and penetrated pesticides of complex matrices [114].

3 | QUANTUM DOTS AND THEIR APPLICATION IN THE ANALYSES OF PESTICIDES AND VETERINARY DRUGS

In the early 1980s, Dr. Alexei Ekimov published the synthesis of a very small semiconductor crystal, and Louis Brus, a researcher at Bell Laboratories in the United States, published a similar finding four years later [115]. Mark Reed named this semiconductor crystal "quantum dots" (QDs) [116]. The technology, which is based on the photoluminescence and electroluminescence phenomena is mainly applied to LCD fields where it is gaining popularity [117]. Presently, there is an increase in the application of QDs in engineering and the other various fields. In 1998, the Alivisatos and Nie groups applied this phenomenon and technology as a new fluorescent probe for biological imaging and detection [118,119]. QDs are colloidal ultrafine semiconductor crystals (generally 2–10 nm in diameter) with unique optical properties due to the quantum confinement effect, which favors the development of new chemical sensors and biosensors [120,121]. With size-adjustable optical characteristics, such as an emission spectrum, there is a shell surrounding a core made of inorganic material, and as a bead, a structure coated with a polymer [120,121] (Supporting Information Figure S2).

The brightness of QDs is 20 times higher than those of organic dyes, and its stability against photobleaching is improved by a factor of 100. Thus, its detection sensitivity and repeatability can be significantly improved compared with those of conventional dyes, especially in complex sample analysis [119]. Therefore, QDs are widely utilized to detect residual antibiotics and pesticides in animals. QD signal styles include resonance Rayleigh scattering (RRS), fluorescence, chemiluminescence, electrochemical luminescence, and photo-electrochemistry. QDs can be used as signal-generating or signal-amplifying elements in sensors and biosensors as well as direct detection method, such as fluorescence method based on quantum dots.

TABLE 1 SERS-detected pesticides/antibiotics, which were analyzed with Ag- and Au-based nanoparticles (AgNPs and AuNPs, respectively) in various matrices

Substrates	Pesticides/antibiotics	Matrix	Limit of detection (LOD)	References
AgNPs	Tricyclazole	Paddy rice	0.002 mg/L	[76]
	Carbofuran	Rice	0.446 mg/L	[77]
	Prometryn	Ultrapure water and tap water	5×10^{-12}, 5×10^{-9} mol/L	[78]
	Paraquat	Apple and pear skin	10^{-9} M	[79]
	Triphenyltin	Apple peels	6.25 ng/cm	[80]
	Phosme	Navel orange skin	1.23 mg/L	[81]
	Chlorpyrifos	Navel orange skin	1.26 mg/L	[81]
	Thiophanate-methyl	Red bell pepper	8 mg/kg	[82]
	Carbendazim	Red bell pepper	8 mg/kg	[82]
	Methamidophos	Red amaranth, little cabbage, Chinese cabbage, leek, spinach, and Chinese little greens	0.01 μg/mL	[83]
	Carbofuran	Soybean	0.520 ppm	[77]
	Penicillin G	Fermentation broths	>50 mM	[84]
	Thiram	Apple, pear, and grape peel	4.6–5.7 ng/cm^2	[85]
	Tetracycline	Whole milk	0.01 ppm	[86]
	Histamine	Fish	(0–200 mg/kg)	[87]
	Crystal violet and malachite green	Fish	(4.1 ng/g, 3.6 ng/g	[88])
	Thiram	Apple, grape, and eggplant	0.53, 0.58, and 0.55 ng/cm^2	[89]
	Tetracycline	Milk	0.01 ppm	[90]
	Paraquat	Adzuki beans	0.8 μg/kg	[91]
	Fenthion	Tomato, pear, and cabbage	0.05 mg/L	[92]
	Dimethoate	Water and olive leaves	5 x 10^{-7} M	[93]
	Tetracycline and dicyandiamide	Milk	1×10^{-9} M and 1×10^{-7} M	[94]
Au NPs/NRs	Chlorpyrifos	Rice	0.506 mg/L	[95]
		Apples (Fuji) surface	0.13 mg/kg	[96]
	Isocarbophosphorate, and imidacloprid, deltamethrin	Tea leaves and apple peels	0.01–0.02 mg/kg	[97]
	Thiram, ferbam	Tap water, apple juice, and vegetable juice	1.78–87.01 nM	[98]
	Difenoconazole	Pak choi	0.4143 mg/L	[99]
	Azinphos-methyl, and phosmet, carbaryl	Apple and tomato	2.91–6.66 ppm	[100]
	Omethoate and chlorpyrifos	Apple	1.63 and 2.64 mg/cm^2,	[101]
	Thiram	Food and environment	10^{-14} M	[102]
	Fonofos, phosmet, and sulfoxaflor	Paddy water	0.25–1.0 mg/L	[103]
	Tetracycline	Duck meat	1.120 mg/L	[104]
	Ediphenphos	Rice	0.1 μg/g	[105]
	Chlorpyrifos and Aldicarb	Animal Feed	1.4 and 9.0 mg/kg, respectively	[106]
Au@Ag NPs	Thiabendazole, ferbam	Liquid milk	0.003–0.12	[107]
	Levofloxacin	Animal husbandry	0.37 ng/L	[108]
	Imazalil	Apple, citrus, and tomato	15.3–114.2 mg/L	[109]
	Thiacloprid		380 μM	[110]

3.1 | Direct detection method: Fluorescence method based on quantum dots

Fluorescence method based on quantum dots is a method of directly detecting residual pesticides and veterinary drugs without employing a sensor. Fluorescence method based on quantum dots adopts the following phenomenon: when two different wavelength ranges of fluorescent materials are adjacent to each other, the energy (donor), which causes one fluorescence, is transferred to the other fluorescent material, thus producing a different acceptor. Briefly, when the difference between the emission wavelength of the energy donor and the absorption wavelength of the acceptor is ˂10 nm, the energy of the electrons excited by the donor may be transferred to the acceptor by a non-radioactive energy-transfer process [123–124].

A list of the pesticides/veterinary drugs that were detected by fluorescence method based on quantum dots is presented in **Table 2**.

3.2 | Quantum dots attached to a sensor

QDs can be applied to biosensors, including sensors containing complex probes or electrodes that are utilized in electrochemistry. Based on specific reactions, biosensors can simplify the analyses of pesticide and veterinary drug residues. The high specificity and sensitivity, as well as the small size and portability of biologically active substances, are advantageous for real-time detections [152]. The classification of various QD-based sensors is, as follows:

QD – enzyme – based, QD – antibody – based,

QD – aptamer (APT), and QD*nonumber*

– molecularly *imprinted* polymer (MIP) sensors.

3.3 | Quantum dots –enzyme-based sensor

The inhibition of acetylcholinesterase (AChE) by carbamate (neostigmine) is an example of the action of a QD–enzyme sensor. In the hybrid method, AChE hydrolyzes acetylcholine into choline, after which the choline oxidase oxidizes choline into betaine, thereby generating H_2O_2, which quenches the CdSe/ZnS QD fluorescence [153]. In the presence of an inhibitor, such as a pesticide or veterinary drug, the biocatalyst (enzyme) cascade (described above) would be stopped. However, the QD fluorescence would remain unchanged; this favors the detection of small molecules [148].

Organophosphate pesticides (OPs) were detected in tap water and food after the evaluation of AChE via the inner filter effect (IFE) between nitrogen-doped carbon dots (N–CDs) and 2,3-diaminophenazine (DAP) [154]. A self-powered biosensor was proposed for the ultrasensitive detection (LOD, 0.012 ng/mL) of OPs via CdS and enzyme inhibitions [155]. Utilizing a glucose meter, a portable onsite detection method for the organophosphorus compound was developed after the inhibition of AChE with LOD of 5 μg/L [156].

3.4 | Quantum dots –antibody-based sensors

The electrochemical signals were employed by a QD–antibody with enhanced sensitivity to detect pesticides and veterinary drugs. The electrochemical electrode and conjugation of the QDs–antibody that was decorated on the surface of the electrode are referred to as the QD–antibody sensor [152]. Salbutamol and clenbuterol were detected by a QD–antibody sensor with LODs of 5.6 and 5.5 ng/L, respectively [157,158]. A fluorescent immunochromatographic strip test coupled with a QD–antibody probe was proposed for the detection of 1-aminohydantoin in animal tissues at LOD of 0.14 ng/g [159].

A QD-fluorescence linked immunosorbent assay (FLISA), which utilizes QDs as the fluorescent probe, has become an essential tool for detecting pesticide and veterinary drug residues. In FLISA, a fluorescent substance is bound to an antibody or antigenic molecule, and the analyte is determined by measuring the change in fluorescence intensity due to a specific reaction between the antigen and antibody [160]. Triazophos, a pesticide, was detected in water, apple, pear, cucumber, and rice at the 0.508 ng/L level by FLISA on CdSe/ZnS QDs [161]. The advantages of QD-FLISA are its simplicity, speed, accuracy, specificity, sensitivity, simple pre-processing, as well as the fact that no special test equipment is required [162].

3.5 | Quantum dot-aptamer sensors

APT is a single-stranded nucleic acid (DNA, RNA, or modified nucleic acid) or peptide molecule, which possesses a stable tertiary structure and can bind to a target molecule with high affinity and specificity. Its etymology is the Latin word, “aptus,” meaning “fitting” [163]. APT is an oligonucleotide sequence with a length of ˂100 nt, which must be sequenced into exhibiting high specificity and affinity for a specific substance [152]. Nowadays, there are numerous applications of QD-APT [164]. Utilizing a QD–APT sensor,

TABLE 2 Detections of pesticides/antibiotics in various matrices by QDs

QD	Pesticides/antibiotics	Matrix	LOD	References
CdTe	Etimicin, isepamicin, and amikacin	Serum and urine	5.1, 2.0, and 25 μg/L, respectively	[125]
	Doxycycline	Honey and human serum	52.90 μg/L	[126]
	Tetracycline and oxytetracycline	Water, honey, and drug	9.78 μg/L 13.81 μg/L	[127]
	Chlorpyrifos	Apple	0.035 μg/L	[128]
	Thiamethoxam, acetamiprid, and imidacloprid	Vegetables	50, 10, and 9 ng/g, respectively	[129]
	Azoxystrobin, kresoxim-methyl, and pyraclostrobin	Fruits and vegetables	2, 1, and 2 ng/g, respectively	[130]
	Loxacin, enrofloxacin, ciprofloxacin, lomefloxacin, and norfloxacin	Milk	4, 7, 8, 7, and 5 ng/g, respectively	[131]
	Rifampicin and rifaximin	Human urine and drug	1500 and 1000 μg/L, respectively	[132]
	Glyphosate	Apple	0.02–2.0 ng/g	[133]
	Chlortoluron	Irrigation water	0.017 μg/L	[134]
CdS	Neomycin and streptomycin	Serum and urine	1.7 μg/L 4.4 μg/L	[135]
	Cloxacillin	Water	5.8 μg/L	[136]
	Dicofol	Water	55 μg/L	[137]
	Pentachlorophenol	Tap water	0.003 μg/L	[138]
CdSe/ZnS	Paraquat	Water	0.003 μg/L	[139]
	Monocrotophos, dichlorvos, parathion, chlorpyrifos, methamedophos, cadusafos, dimethoate, terbufos, and ethion	Tomato	0.0967 μg/L	[140]
CdTe/CdS	Polymyxin B	Drug	6.36 μg/L	[141]
CdTe-AuNP	Acetamiprid	Water, soil, and rice	16.8 μg/L	[142]
	Parathion-methyl	Tap water, milk, and rice	0.018 μg/L	[143]
Cds/Cu	Thiophanate-Methyl	Apple and tomato	2.90×10^{-6} μmol/L	[144]
Cds/Qy	Tetracycline, chlorotetracycline, and oxytetracycline		5.18, 14.00, and 6.06 nmol/L, respectively	[145]
AuNCs.MnO_2	Thiacloprid, nitenpyram, acetamiprid, imidaclothiz, thiamethoxam, cypermethrin, fenpropathrin, tebuconazole, chlorfenapyr, and carbaryl.		0.125–1 μg/L	[146]
N-CQDs	Oxytetracycline	Tap water, lake water, and soil	0.077 and 0.973 μmol/L	[147]
ZnO QD	Atrazine, glyphosate, and aldrin, tetradifon	Water		[148]
MNP–SiO2–QD	Doxycycline	Egg albumin and bovine serum albumin (BSA)	0.02–1 mg/mL	[149]
CDs	Diazinon, amicarbazone, and glyphosate		0.25–2 ng/mL	[150]
β-CD-MoS2 QDs	Parathion-methyl	Fruits and vegetables	3.3 ppb	[151]

acetamiprid was detected at LODs of 0.7 and 7.29 nM [165,166], oxytetracycline was detected at LODs of 0.1 and 1.9 nM in honey water and a milk sample by Ag nanoclusters (AgNCs) and AgNPs, respectively. Oxytetracycline was also detected in water at a level of 25 μg/L by a GO hydrogel [167–169]. Furthermore, kanamycin was detected in milk by AuNPs and MoS_2 nanosheets with LODs of 18 nM and 1.1 μM, respectively, and in human serum by CuS NPs [170–172] at an LOD of 26 pM. An ultrasensitive method successfully detected kanamycin in animal serum and raw milk with LOD of 1 pM utilizing a reduced GO-based fluorescent aptasensor [173]. Tetracyclin was detected at an LOD of 0.95 ng/mL in animal-derived food utilizing nitrogen-doped graphene QDs (N-GQDs) and 0.06 ng/mL in milk utilizing vanadium(IV)disulfide QDs (VS2 QDs) and molybdenum(IV)disulfide (MoS_2) nanosheets [174,175]. Florfenicol was detected in milk at LOD of 5.75 nmol/L utilizing the magnetic beads-based SELEX (systematic evolution of ligands by exponential enrichment) technique with high binding affinity [176]. Furthermore, profenofos, phorate, isocarbophos, and omethoate were determined in vegetables at LODs of 0.003, 0.3, 0.03, and 0.3 nM, respectively, by the one-step co-electrodeposition of aptamer and GO–CuNPs nanocomposite [177]. Employing an AuNP-based fluorescent aptasensor, ofloxacin was detected at an LOD level of 1.66 μg/L in milk [178]. Enrofloxacin was detected in milk with an LOD of 3.7 nM by GO [179].

3.6 | Quantum dot– molecularly imprinted polymer sensors

QD–MIP refers to a polymer with specific selectivity, which originates from immunology, for a target molecule (detection substance). Put differently, it refers to a polymer with a specific selectivity for a specific type of target molecule (detection material) [180]. High-selectivity MIP is synthesized on a QD surface with special optical properties, and QD is generally modified by a silylating agent or mercaptan carboxylic acid and a surfactant, thereby forming a surface where MIP can be easily performed [181].

The QD–MIP sensors are employed to selectively identify and detect pesticide and veterinary drug residues [152]. For instance, it has been employed to detect pentachlorophenol and chlorpyrifos in river water at LODs of 22.91 and 5.96 μg/L, respectively [182,183]. Cypermethrin was detected at an LOD of 6.7×10^{-14} M in the soil, mackerel, crayfish, and water [184]. Based on previous studies, In addition to direct detection methods, QDs can be assembled into biosensors with different materials, such as QD–enzyme, QD–antibody, QD–aptamer, and QD–MIP sensors, for detection. Therefore, if the QD probe is constructed appropriately, it can be widely applied to detect relatively large (nucleic acids, proteins, and enzymes) and small chemical molecules [185]. QDs offer a very high specific detection for target substances. Therefore, improved investment toward developing various QD-biosensors should be considered.

4 | BIOSENSOR AND ITS APPLICATION IN PESTICIDES AND VETERINARY DRUGS ANALYSIS

Between 1909 and 1922, a method for immobilizing proteins (invertase) on charcoal was developed. An oxygen electrode, viz. "Clark electrode," which was considered as the first true biosensor, was developed in 1956. Further, a glucose sensor, which was an electrochemical enzyme electrode, was developed in 1962 [186–188]. A biosensor is an analytical device that combines a "biological element" and "physical and chemical detectors (biotransducers). It is a stand-alone analytical device that generates a measurable signal for the detection of biologically valuable analytes [189,190]. The mechanism of the enzyme-based biosensor is shown in Supporting Information Figure S3.

Thus, by exploring the property of a bioreceptor (antibody, enzyme, DNA, RNA.), which facilitates its selective reaction or binding with a specific substance, e.g., an antibiotic), the presence of a specific substance can be confirmed by a signal converter. Biosensing elements are a set of biological entities that can react or combine with a specific group of compounds to produce a detectable signal. The most utilized biosensing elements are the catalyst- and affinity-type biosensors. A catalytic sensor is composed of enzymes, microorganisms, organelles, cells, or tissues, and an affinity sensor is composed of an antibody, receptor, and nucleic acid [191].

A novel electrochemical immunosensor, which is based on a bio-microelectromechanical system (Bio-MEMS), was developed to screen tetracycline in honey [192].

5 | IMMUNOASSAYS FOR DETECTING PESTICIDES AND VETERINARY DRUGS

Employing the antigen–antibody specific binding reactions, the immunoassay is a frequently employed analytical method for detecting pesticides and veterinary drugs [193]. There are five types of labeled immunoassays: radioimmunoassay (RIA), fluorescence immunoassay (FIA), chemiluminescence immunoassay (CLIA), enzyme-linked immunoassay (ELISA), and bio-barcode immunoassay, and they are employed as biosensing analytical tools [194,195]. Among them, the enzyme-based

TABLE 3 Multiresidue immunoassays for detecting pesticides and veterinary drugs

Method	Pesticides/antibiotics	Matrix	LODs	References
ELISA	Organothiophosphate and organophosphate pesticides	Food	0.018–0.135 and 0.013–0.171 μg/mL, respectively	[197]
	Chlorpyrifos and fenthion	Tangerine juices	0.20 ± 0.04 and 0.50 ± 0.06 μg/L, respectively	[189]
	Clindamycin and lincomycin	Animal tissues	1.8 and 6.8 μg/kg, respectively	[198]
	Penicillin G, amoxicillin, ampicillin, penicillin V, cloxacillin, oxacillin, cloxacillin, carbenicillin, dicloxacillin, and methicillin, nafcillin	Milk	0.7–9.3 μg/kg	[199]
	Permethrin, aroclor1248, and aroclor1254	Soil/sediment and house dust	1.5–14.3 μg/kg	[200]
	Sulfonamides (sulfamonomethoxine, sulfamethoxazole, sulfaquinoxaline, sulfadimethoxine, and sulfamethazine)	Milk	1.00–6.10 μg/L	[201]
	chloramphenicol, avermectin, tetracycline, and streptomycin	Food	0.106–0.134 ng/mL	[202]
	Ethylene thiourea	Soil, tomato, and potato	0.201 ng/mL	[203]
	Trimethoprim, diaveridine, brodimoprim, and ormetoprim, baquiloprim	Chicken and milk	0.06–0.8 μg/kg 0.05–0.6 μg/L	[204]
		Milk, eggs, chicken, and pork	0.208–9.24 ng/mL	[205]
CLIA	Parathion, methyl parathion, and fenitrothion	Grains, fruits, and vegetables	1.24–5.57 μg/kg	[206]
	Fenpropathrin, deltamethrin, and λ-cyhalothrin	Orange, eggplant, and cowpea	0.18–0.39 ng/mL	[207]
FIA	Streptomycin, tetracycline, and penicillin G	Milk	5 × 10–3 μg/kg	[208]

biosensors for analyzing pesticides and veterinary drugs have attracted tremendous interest owing to their fast response, reliability, selectivity, and high sensitivity [196]. A list of representative pesticides and veterinary drugs, which were determined by various immunoassays, is presented in **Table 3**.

Owing to its rapid onsite analysis capability, enzyme-based biosensors have attracted increased and continuous scientific attention. The preparations of a broad-specificity antibody and multiple antigenic determinants, as well as multi-residue detections via fluorescent-labeled antibody/antigen, are the three key points of multi-residue analyses. The combination of these two methods can extend the scope of detection. Through technological advancements, immunoassays have also been updated with new technologies. APT technology is one of the updates; it restores the classical pattern by binding the antibody specifically to the target analyte [209]. Moreover, to enhance signal and sensitivity, additional nanotechnologies, such as carbon materials, AuNPs, and QDs, must be introduced into immune technology.

6 | ION MOBILITY-MASS SPECTROMETRY AND ITS APPLICATION IN PESTICIDE AND VETERINARY DRUG ANALYSES

IM spectrometry (IMS) is a simplified version of MS, which was first introduced more than 70 years ago and called plasma chromatography [205]. IMS is an analytical tool, which separates and identifies ionized molecules in the gas phase based on their mobility in a carrier buffer gas [210]. IMS consists of three devices that are maintained at atmospheric pressure: (a) an ionization source, (b) an ion drift tube, and (c) a detector (it is maintained with a positive or negative uniform electric-field gradient). As shown in Supporting Information Figure S4A, the measurement process employing the IMS method includes the following: (a) the ionization process, which generates the reactive ions from an ionization source, (b) the reaction process in which the reactive ions react with the target component molecule (analyte) to generate new ions (product ions), (c) the rearrangement process in which the generated cations

TABLE 4 Determination of pesticide and veterinary drug residues in various matrices via IMS

Method	Pesticides/antibiotics	Matrix	LOD	References
D™S	Atrazine	Natural water samples	287.57 mg/L	[222]
	Prosulfuron, rimsulfuron, tribenuron-methyl, metsulfuronmethyl, thifensulfuron-methyl, primisulfuron-methyl, triasulfuron, and sulfometuronmethyl	River water samples	0.85–5 mg/L	[223]
	Simazine, acetamiprid, hexazinone, paclobutrazol, amitraz, clofentezine, and boscalid	Pulp and peel of an apple, cucumber, and cherry tomato	1–3 mg/kg	[224]
	Chloramphenicol	Water, milk, honey, and urine samples	0.1 mg/L	[225]
	Tetracycline	Human plasma and urine	50–100 mg/L	[226]
	Phosalone and diazinon	Pistachio	0.1 and 0.5 ppm	[227]
FAIMS	Aldicarb, diazinon, dimethoate, and parathion	–	6.08–746.0 mg/L	[228]
	Sulfotep, propoxur, and nicotine	–	6.4–32.4 mg/L	[229]
DMS	1,2,4-Triazole and its metabolites (1,2,4-triazole alanine, 1,2,4-triazole acetic acid, and 1,2,4-triazole lactic acid)	Cucumber, orange, polished rice, and whole milk as the main investigated matrices	10 mg/kg	[230]

and anions are rearranged, (d) the separation process in which each ion is separated according to the movement of ions, and (e) the detection process in which the ions are detected by a detector [211]. Further, Supporting Information Figure S4B shows the specifications of a commercial portable IM spectrometer.

Initially, military agencies in the United States and the United Kingdom utilized this instrument for surveying human activities in Vietnam [212]. Through continuous research and developments, IMS has grown into a powerful, attractive, inexpensive analytical tool with reduced LODs, as well as high selectivities, sensitivities, and portabilities [213]. Although IMS was previously employed to detect chemical warfare agents (CWAs), its application range has been expanded to environmental monitoring and food safety owing to its onsite detection and portability [214–217]. Moreover, a portable IM spectrometer is employed to monitor chemical weapons, explosives, airport security, air quality, proteomics, and agrochemicals and drugs [211]. A portable IM device with its specifications is shown in Supporting Information Figure S4B.

The IMS approaches employed for chemical and biochemical analyses include the field drift tube IMS (DTIMS), differential mobility analysis (DMA), high-field asymmetric IMS (FAIMS), and traveling wave IMS (TWIMS) [218–221]. The various pesticides and veterinary drugs that have been detected by IMS are listed in **Table 4**.

7 | MINIATURIZED GC: A PROSPECTIVE TOOL FOR ANALYZING PESTICIDES AND VETERINARY DRUGS

GC is a powerful analytical instrument in the fields of analyzing pesticide and veterinary drug residues. The revolution of microfabrication technology has emerged in the fields of computing, signal processing, as well as in the productions of smartphones, televisions, signal processing, and in the automobile industry since the last few decades [231]. Therefore, the miniaturization of large analytical instruments is necessary for portability, as well as for onsite detection. MEMS technology can resolve the miniaturization challenges of analytical instruments and afford small, energy-efficient, and less-expensive systems (Supporting Information Figure S5) [232].

The basic working principles of a conventional GC and a miniaturized or micro-GC are similar, although the micro-GC is smaller. Therefore, the power consumption of a micro-GC is low, and its analytical speed is high [233].

A MEMS-based six-valve injector with a 250-nL injection volume was used in the micro-GC. Each valve was composed of polyether ether ketone (PEEK) membranes, which were sandwiched in a silicone substrate and glass. The six valves were opened and closed through the actuation hole by changing the pressure [234]. The separation part is the most critical part of any GC system. For miniaturized GC, the chip-based microcolumns were prepared by MEMS technology [233]. In addition to the

conventional capillary column, the small-sized microcolumns consumed very low power, although it achieved rapid analysis [233]. A resistive heating technology in which an electric current passes through a conductor is applied for microcolumn heating [235].

Various micro-detectors are utilized in miniaturized GC, such as a thermal conductivity detector (TCD), surface acoustic wave (SAW) device, chemiresistor array, chemicapacitive sensor array, nanocantilever, PID, FID, ECD, and IMS [233]. Regarding the analysis and separation of complex mixtures, semi-packed and multi-capillary columns have been developed to increase the separation efficiency and peak resolution. Multidimensional micro-GC was also introduced to achieve improved peak separation and the resolution of complex mixtures. Adorned with several microfabricated components, a portable micro-GC system has now been commercialized for the routine analyses of complex solutions. In most published studies, simple hydrocarbons were separated by micro-GC systems under laboratory conditions. Therefore, increased attention and research are required to further develop this portable GC system for the analyses of environmental pollutants.

8 | CONCLUDING REMARKS

In the past, computers, televisions, and mobile phones were bigger. However, with technological advancements, they have become smaller, fashionable, and easy to handle. The analyses of pesticides and veterinary drug residues still require early-aged computer-sized instrumentations, time-consuming complex sample preparations, and highly skilled researchers. Moreover, it is still challenging to determine the real scenario of contamination in field samples because of the probability of degradation during the long detection procedure. There are many strategies for developing robust methodologies for onsite/on-field detections. Soon, table food can be scanned instantly to check for agrochemical contaminants with a laser beam and a simple app on a smartphone.

CONFLICT OF INTEREST

The authors have declared no conflict of interest

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ORCID

Jae-Han Shim https://orcid.org/0000-0002-5361-2903
A. M. Abd El-Aty https://orcid.org/0000-0001-6596-7907

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AUTHOR BIOGRAPHIES

Md. Musfiqur Rahman, is a Lead Researcher at Jeonnam Bioindustry Foundation, and Adjunct Research Associate at Natural Products Chemistry Laboratory, Chonnam National University, Gwangju, Republic of Korea. He is an author/co-author of more than 80 article published in prestigious International Journals with good impact factors. He is also an author of four review articles and three book chapters.

Dong Ju Lee, is a Senior Researcher, at Institute of Basic Sciences, Chonnam National University. During his research career he was involved as a Researcher at various institutes. As a Research associate he worked in Michigan State University, as a Research Professor at Chonnam National University and as a Senior Researcher at Seoul National University. Plant Molecular genetics is his area of Research.

Ara Jo is presently working as a Researcher at Natural Products Chemistry Laboratory, Chonnam National University, Gwangju, Republic of Korea. She completed her master's degree from Department of Biological Science and Biotechnology, focusing research on molecular genetics. Now she is working on pesticide residue analysis funded by Ministry of Food and Drug Safety.

Seung Hee Yun is a Researcher of Natural Products Chemistry Laboratory. She majored in Agricultural Chemistry at College of Agricultural and Life Sciences, Chonnam National University. Now she is working on pesticide residue analysis project with Professor Jae-Han Shim.

Jong-Bang Eun. is a Professor in the Department of Food Science and Technology at Chonnam National University in Gwangju, Republic of Korea. Eun received his Ph.D. in Food Science and Technology with Biochemistry Minor from Mississippi State University in 1991. Dr. Eun's research program focuses on food processing and preservation, effect of functional ingredients/nutraceuticals and new product development in food. Dr. Eun has published more than 200 original scientific papers in peer-reviewed journals presented more than 450 abstracts at the conferences and symposiums. He has also published 1 book and 5 book chapters.

Hyeog-Hyeog Im, is a Professor at Department of Food Engineering, College of Engineering, Daegu University. His research interest is Risk assessment of residue pesticide and Veterinary drug in Food, Maximum Residue Limit of residue pesticide and Veterinary drug and Food Analytical method development of residue pesticide and Veterinary drug in Food.

Jae-Han Shim is a Distinguished Professor and Rector of Natural Products Lab, Chonnam National University, Gwangju, Republic of Korea. He is among the board member of Biomedical Chromatography, Journal of Separation Science and Food Chemistry. He

published more than 300 articles in International Journals with interest of pesticide residue analysis in agricultural crops.

A. M. Abd El-Aty is a Professor of Pharmacology, Cairo University, Egypt. His era of interest is "Food Science and Technology"; in particular, xenobiotic analysis using various extractions as well as analytical methods. He published > 300 articles in prestigious journals, with current *h*-index = 32. He is a member of 2017–2021 Expert Roster of the Joint (FAO/WHO) Expert Committee on Food Additives.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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