Int. J. Electrochem. Sci., 17 **(2022)** Article Number: 22019, doi: 10.20964/2022.01.07

International Journal of
ELECTROCHEMICAL
SCIENCE
www.electrochemsci.org

Mini Review

Recent Advances and Future Prospects of Aptamer-based Biosensors in Food Safety Analysis

Yue Wang[1], *Hongguo Zhai*[1] ,*Jiaqi Yin*[1], *Qi Guo*[1], *Yuhao Zhang*[1], *Xia Sun*[1], *Yemin Guo*[1], *Qingqing Yang*[1] , *Falan Li* , *Yanyan Zhang*[1,2,3,*]

[1] School of Agricultural Engineering and Food Science, Shandong University of Technology, No.12 Zhangzhou Road, Zibo 255049, Shandong Province, China.
[2]Shandong Xicheng Agricultural Machinery Technology Co., Ltd., Shandong Province, China.
[3] Shandong Sider Agricultural Equipment Co., LTD., Shandong Province, China.
[*]E-mail: zyyan1104@163.com

Received: 22 September 2021 / *Accepted:* 27 October 2021 / *Published:* 6 December 2021

The problem of environmental pollution and food security have brought global attention to food safety issues. Pollutant detection is one of the significant missions in the background of serious global environmental problems. Heavy metal ions, pesticides, biotoxins, and antibiotics on sites are in high demand in environmental analysis. As a simple, accurate, inexpensive, and selective detection method, aptamer-based biological sensors are very suitable for environmental detection and food safety analysis. This review principally summarizes the recent advances in the use of aptamer-based fluorescence sensors for food safety detection. This includes the detection of divalent metal ions, trivalent metal ions, pesticide leftover, biotoxins, and antibiotics.

Keywords: Biological aptamer sensors, Food safety, Heavy metals, Pesticide residues, Biotoxin, Antibiotics

1. INTRODUCTION

Food safety and environmental pollution are the primary global problems affecting sustainable human development [1-2]. There are many kinds of food pollutants, for example, heavy metal ions, pesticides, biotoxins, and antibiotics, and these pollutants have become the focus of global research [3-4]. Organophosphorus (OP) pesticides are highly toxic to humans [5]. For example, chlorpyrifos (CP) can cause serious health problems such as pulmonary oedema, incontinence and coma [6]. Antibiotics are a class of secondary metabolites that can interfere with the development of other living cells, and can be produced and secreted from higher animals, plants, or microorganisms [7-8]. Thus, heavy metal ions, pesticides, biotoxins, and antibiotics exist widely in agriculture, industry, and other areas. These

substances can enter the human body through the food chain and have adverse effects on the human body [9]. With the continuous deposition in the human body, heavy metals gradually affect the various organs of the human body and most commonly heavy metals can damage the kidneys, liver, and bones [10]. Heavy metal ion, biotoxin, antibiotics, and pesticide residue detection is an indispensable basic link and requisite for food safety and environmental pollution control [11-12]. With the development of science and technology, detection technology is gradually developing towards the direction of simple and efficient, high sensitivity and accuracy, fast and cheap, flexible and practical, all of which are demanded for detection are urgent needed globally [13].

Atomic absorption spectrometry (AAS), ultraviolet-visible spectrometry (UV-VIS), inductively coupled plasma mass spectrometry (ICP-MS), gas chromatography (GC), high-performance liquid chromatography (HPLC), mass spectrometry (MS) and atomic fluorescence spectroscopy (AFS) are the common methods used in the field for analyzing biotoxins, antibiotics, heavy metal ions, and pesticide residues [14-16]. These traditional methods have good detection accuracy, but they require a long time to detect target objects and they are relatively cumbersome in operation [17]. Therefore, simple, rapid and sensitive detection methods have become the focus of research.

As sensitive and fast detection tools, sensors have been used in many cross-disciplinary sciences [23]. With the development of sensors, fluorescent sensors and electrochemical sensors have successively emerged. These sensors have the advantages of high sensitivity and high specificity [24-25]. Among them, the combination of sensors and aptamers is a new detection technology. The aptamer is a small oligonucleotide sequence screened in vitro, and this screening process is called exponential enrichment (SELEX) [18−19]. Aptamers can bind with high affinity and specificity to small molecules and various types of targets [20−22].

For these sensors, biological aptamer sensors are more particularly interesting, the primary cause is that the high sensitivity and feasibility of quantification [26]. However, most fluorescent aptamer sensors are attached to fluorescent substances and quenchers (mainly attached to the active sites or 3' and 5' ends of the aptamer) [27-28]. An electrochemical sensor is a device that converts chemical signals into electrical signals. In this article, we summarize aptamer-based fluorescence and electrochemical sensors used in food safety applications. We offered readers the high-impact and achievements of aptamer-based biological sensors from our point of view, which provided comprehensive coverage of the current status. In addition, this review discussed in detail the existing inadequacies and challenges of aptamer-based biological sensors.

2. CLASSIFICATION AND PRINCIPLE OF ELECTROCHEMICAL SENSORS

2.1 Classification of electrochemical sensors

Electrochemical biosensors can be divided into current-type, impedance-type, potential-type and conductivity-type sensors. The sensitivity and selectivity of electrochemical sensors depend mainly on biometric elements. Aptamers as biometrics have become the focus of electrochemical sensor research. Electrochemical adaptor sensors can be divided into labeled and unlabeled sensors according to whether markers are used to generate detection signals [29].

2.1.1 Labeled electrochemical aptamer sensors

Labeled electrochemical adaptor sensors label some functional markers with electrochemical or catalytic activity on the adaptor probe end by physical adsorption, chemical modification and other methods and change the configuration to change the electrochemical signal.

Xu's [30] team put forward a new type of electrochemical biosensor. The sensor was a trigger loop amplifier and triggered a hybrid chain reaction at hairpin-shaped fit 3 'end of the S1 and S2 chain and the 5' end of modified methylene blue signal molecules. This type of electrochemical adapter sensor can sensitively and selectively detect Hg^{2+}. Under optimum conditions, the sensor detection limit was as low as 1.6 pM.

2.1.2 Unlabeled electrochemical aptamer sensors

The unlabeled electrochemical adaptor sensor does not need to label the electroactive substance on the adaptor probe and detects directly detects according to the interaction between the target substance and the adaptor. After the aptamer interacts with the target substance, the conformation of the aptamer changes, and the target substance can be detected according to the signal changes.

In 2020, Lu [31] developed an electrochemical adapter sensor for the detection of mucin protein 16 (MUC16). There was no modification of the adapter probe, and an antibody/MUC16/adapter sandwich structure was formed by capturing the target substance mucin 16 and the nanomaterial by the antibody modified on the electrode, which is used for the highly selective detection of MUC16. The detection limit for mucin 16 was 0.02 unit/mL.

In 2021, Nan [32] constructed a labeled electrochemical aptamer sensor based on amino aptamers and thioadapters. This paper mainly studied the detection performance and electrochemical performance of amino aptamers and thioadaptors, which were of great value for the subsequent application of aptamer.

2.2 The principle of electrochemical sensors

Electrochemical biosensors are composed of biometric elements and signal transducers. The detection principle of the electrochemical sensors is to express the interaction signals of target substances and biomolecules in the form of electrical signals and achieve quantitative detection of target substances according to the transformation of electrical signals.

The electrochemical aptamer sensor identifies the components through the combination of the target substance and the aptamer and converts the binding signal of the aptamer to the target substance into an electrical signal to realize the detection of the target substance.

3. CLASSIFICATION AND PRINCIPLE OF THE FLUORESCENCE SENSORS

3.1 Classification of the fluorescence sensors

According to the different fluorescence responses of the fluorescent sensor combined with specific analytes, these sensors mainly divided into fluorescence and quenching. There are three types of fluorescence sensors: enhancement (turn on), quenching (turn off), and ratio [33-34].

3.1.1 "Turn on" fluorescence sensors

"Turn on" fluorescence sensors are common sensors for the detection of target objects. In other words, when combined with target objects, enhanced fluorescence responses are obtained via the different reactions between the fluorescent material and the target objects.

Based on the above tenet, Ma [35] devised and assembled AIEgen (aggregation-induced emission fluorogen)-labeled fluorophore-based IFN-γ (interferon-gamma) fluorescent sensors. These fluorescent sensors were made up of an IFN-γ aptamer probe. This probe was able to localize intracellular IFN-γ at a low concentration <10 pg/mL. The IFN-γ aptamer should have a typical feature: aggregation-induced emission (AIE). As shown in Fig. 1, the aptamer only exhibited weak fluorescence. After encountering IFN-γ, the colour of the aptamer showed a strong red colour. This special aptamer displayed an intense fluorescence response due to a the typical aggregation-induced emission of the IFN-γ aptamer. Additionally, the aptamer has been verified to be a highly selective and sensitive probe for IFN-γ with a detection limit as low as 2 pg/mL. At present, this probe has been successfully used for real-time bioimaging.

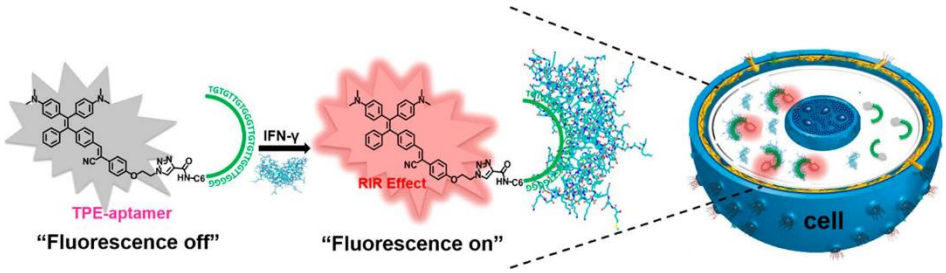

Figure 1. Schematics of the AIEgen-based fluorescent aptasensor for detecting intracellular IFN-γ. [35]. [Reprinted with permission from{ "Turn-on" Fluorescent Aptasensor Based on AIEgen Labeling for the Localization of IFN-γ in Live Cells}, Copyright{2018} American Chemical Society.]

Zhang [36] used C-PS2.M-DNA-templated silver nanoclusters in a turn-on fluorescent biosensor to detect Pb^{2+}. The detection principle is that the lead ions interact with the aptamer, causing the aptamer to fold and form a G-quadruplex, which brings the two ends of the aptamer close together, resulting in fluorescence. This sensor system showed a simple, low-toxicity, selective, and sensitive application for detecting Pb^{2+} in environmental systems. Other turn-on sensors that have been reported in addition to those introduced in this paper including many constructed sensors. Therefore, this type of fluorescence sensor has been extensively studied.

3.1.2 "Turn off" fluorescence sensors

"Turn off" fluorescence sensors are another common type of sensor for the detection of target objects. In other words, when combined with target objects quenching fluorescence responses occur via the different reactions between the fluorescent material and the target objects. Before adding the

detection substance, the fluorescence aptamer sensor will have a strong fluorescence signal. When the target objects are combined with the sensor molecule, the fluorescence intensity will be reduced or even completely quenched. Compared with "turn on" fluorescence aptamer sensors, this type of sensor has high sensitivity, selectivity, and application value.

Utilizing the same design method as in "turn off" fluorescence sensors, Van Dien Dang [37] constructed a turn-off fluorescent biosensor to detect Cu^{2+} and ciprofloxacin (CIP). In this paper, the detection of ciprofloxacin and Homoion was carried out by using a label-free probe and bipyridine. Nitrogen-doped carbon quantum dots prepared by the hydrothermal method were used as probes. As shown in Fig. 2, in the presence of Cu^{2+} and CIP, there was an obvious fluorescence signal change from "on" to "off" to "on", with remarkable selectivity and high sensitivity. Over time, this sensor was able to simultaneously detect Cu^{2+} and CIP from a complex environmental system.

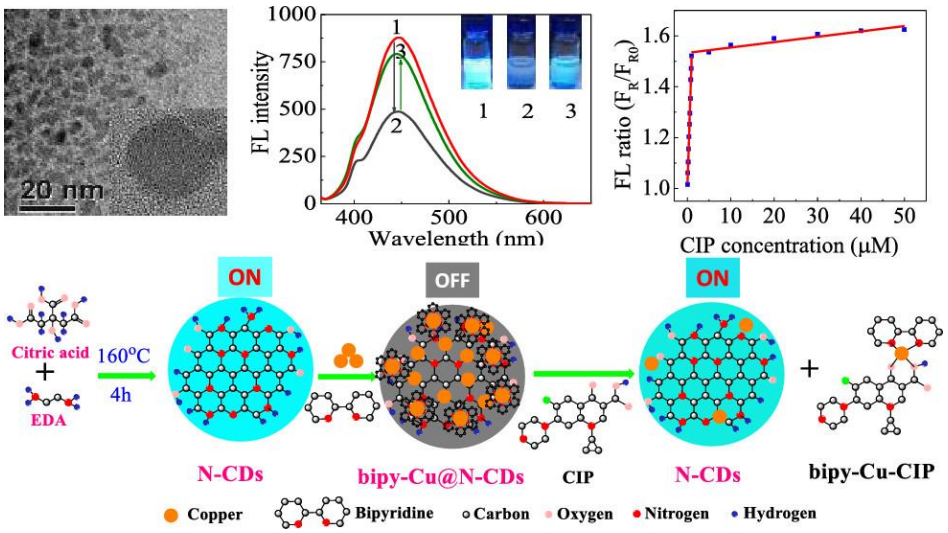

Figure 2. Schematic diagram of detecting Cu^{2+} and CIP. [37]. [Reprinted with permission from{Bipyridine- and Copper-Functionalized N-doped Carbon Dots for Fluorescence Turn Off−On Detection of Ciprofloxacin}, Copyright{2020} American Chemical Society.]

Another bifunctional fluorescence sensor selenium (IV) was designed and characterized by Anupma Thakur [38]. A new method for the detection of selenium (IV) in water based on selenium-induced crosslinking of Sn-doped carbon quantum dots (CQDs) was reported. A sharp decrease in the fluorescence of selenium (IV) was observed in CQDs. Using citric acid and stannous chloride as raw materials, CQDs were prepared by microwave-assisted pyrolysis. Additionally, the detection range for selenium (IV) was 10-1000 ppb. The fluorescence quenching was induced by the Sn CQDS.

3.1.3 "Rationmetric" fluorescence sensors

After the target analyte is added, it reacts with the sensor molecules, and the emission wavelength changes usually producing two fluorescence emission peaks, and the intensity of the two fluorescence

emission peaks is proportional to attenuation or enhancement [39]. This kind of sensor can reduce background interference and other accidental factors and is more widely used. This type of sensor has a high application value.

In 2020, An [40] based on carbon dots/SiO_2 and gold nanoclusters devised an ultrasensitive turn-on ratiometric fluorescence sensor to detect Ag^+. This emission fluorescent probe (CSA) has two emission sites at 448 nm and 610 nm under a single excitation at 380 nm. The enhancement of the fluorescence intensity of Ag NCs mainly occurred after the addition of Ag^+, which could be quantitatively detected in the range of 0-0.1 μM. The detection limit of Ag^+ was 1.6 nM. The principle of Ag^+ detection was as follows: with the addition of Ag^+, the Au NCs fluorescence increased. In addition, the CSs fluorescence was unchanged. Therefore, in the CSA ratio fluorescent probe, quantitative detection of Ag^+ was based on the principle of a ratio fluorescence sensor. This work presented was the first to present a fast, accurate, highly selective, and highly sensitive fluorescence sensor to detect Ag^+.

A near-infrared ratiometric fluorescent probe was made by Zhang [41]. This paper reported a near-infrared ratio fluorescence probe PBT with aggregation-induced emission (AIE) characteristics that was developed for the determination of hydrazine. The recognition site of the sensor is 2-benzothiazolylacetonitrile. The detection principle is as follows: light at 690nm is emitted by the probe, the probe is converted into hydrazone after reacting with hydrazine, and the fluorescence is quenched. In 2021, utilizing a similar principle to that described above, Li [42] constructed a novel barbituric-based fluorescence ratiometric sensor. It was applied to detect cyanide anions. Even if there are other competing anions, it also showed high selectivity and anti-interference.

3.2 The principle of fluorescence sensors

The response mechanism of the fluorescence sensors includes photoinduced electron transfer (PET), intramolecular charge transfer (ICT), fluorescence resonance energy transfer (FRET), excited-static intramolecular proton transfer (ESIPT), and excimers so on. The following will introduce and illustrate the common detection mechanisms.

3.2.1 Fluorescence resonance energy transfer (FRET)

Fluorescence resonance energy transfer is a nonradiative energy transfer process that occurs over nanometre-scale separations (up to 10 nm) between a donor and an acceptor, often called a “FRET pair”. FRET is one of the most powerful phenomena for explaining molecular interactions [43]. In short, FRET is based on the energy transfer between donor and acceptor fluorophores with proximity of 10-100 °A[44].

As shown in Fig. 3, based on the principle of FRET, Ahmad Afzalinia [45] devised a fluorescent biosensor for oligonucleotide-based “sandwich” hybridization. In the presence of complementary chains, La(III)-metal-organic frameworks (MOFs) and silver nanoparticles were quenched by fluorescence

resonance energy transfer. The developed biosensor has high sensitivity (LOD of 0.0386 ppb), high selectivity, and good applicability in clinical sera.

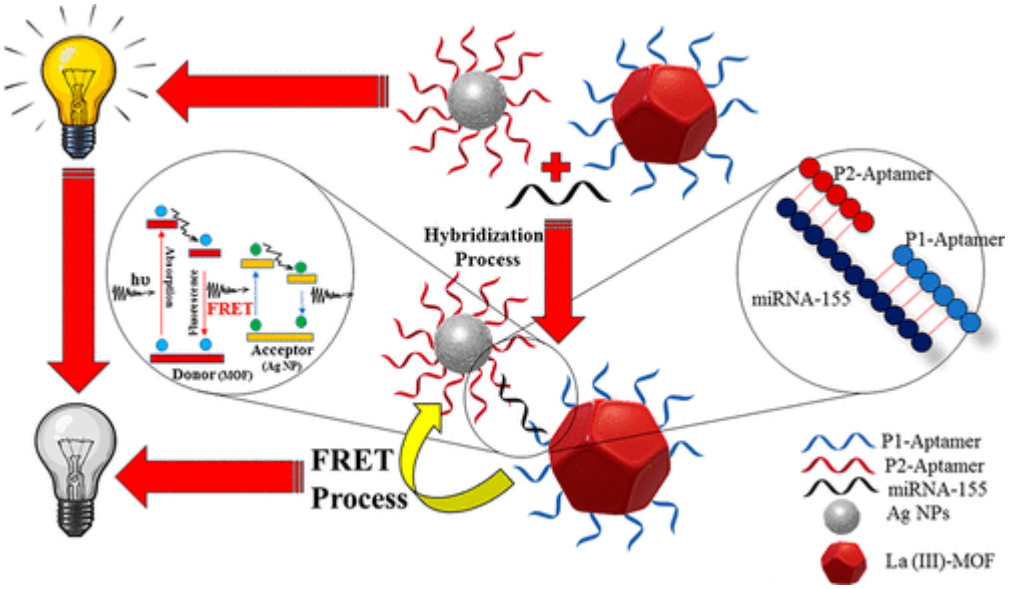

Figure 3. Schematic diagram of photoluminescence quenching-based detection of miRNA-155 as a cancer biomarker by the FRET process. [45]. [Reprinted with permission from{Ultrasensitive Fluorescent miRNA Biosensor Based on a "Sandwich" Oligonucleotide Hybridization and Fluorescence Resonance Energy Transfer Process Using an Ln(III)-MOF and Ag Nanoparticles for Early Cancer Diagnosis: Application of Central Composite Design}, Copyright{2020} American Chemical Society.]

In 2020, an unusual example using tap water and matcha samples was reported by Chen [46]. In this paper, a high-sensitivity fluorescence sensor was developed for the determination of malathion. Researchers have used nanofluorophores and cationic polymer-encapsulated gold (GNPs) as labels for aptamer modification. The sensor has the ability to selectively recognize of malathion, with a detection limit of 1.42 nM.

3.2.2 Photoinduced electron transfer (PET)

The response mechanism of photoinduced electron transfer is fluorescence quenching. The fundamental concept is fluorophore-spacer-receptor molecular engineering [47]. The first requirement for device performance is to excite the fluorophore via the power source and then transfer the electrons to the lowest molecular orbital (LUMO) [48].

Research on fluorescent sensors was conducted by or under the supervision of Mehdi Sheikh Arabi [49]. Based on the principle of PET, a method of carbon fluorescence based on the action of dopamine was designed and synthesized. PET occurs because laccase oxidizes dopamine-modified

carbon nitride to dopaquinone, which causes PET to proceed between dopaquinone and carbon nitride. The sensor has a low detection limit of 2.0 U/L.

Specifically, utilizing PET and aggregation-induced emission, Chen [50] proposed a method of preparing a fluorescent probe. A new fluorescent sensor was designed to detect the salicylaldehyde skeleton. The test results provided a reference for a subsequent practical application. The sensor showed good accuracy, high selectivity, and sensitivity, exhibiting excellent applications in detection. This study provided a new strategy for the detection of the salicylic acid framework, which combines this sensor with fluorescence imaging technology.

3.2.3 Intramolecular charge transfer (ICT)

For intramolecular charge transfer sensors, fluorophores and receptors are usually directly connected by conjugated groups to form a system of large Π bonds, in which two functional groups usually act as electron donors (e.g. -OH, $-NH_2$, etc) or electron acceptors (e.g. -CHO, -CN, etc.) at opposite ends of the molecule [51-52]. The addition of an analyte can result in preferential bonding of groups in the electron donor or acceptor region, resulting in a change in donor-acceptor dipole strength, which is usually associated with a change in intensity and a spectral shift [53-54].

Intramolecular electron transfer is a common detection method in research. Yu [55] used this method to make coumarinocoumarin a fluorescent probe. This probe used PET and ICT to identify the cysteine. The designed probe molecule can reach the maximum TPA (tissue plasminogen activator) in the range of 700-1000 nm, effectively avoiding the factors of self-fluorescence and background interference in biological tissues. The authors hoped it would be convenient for detecting cysteine in the human body.

In 2020, Mahantesh Budri [56] designed a dual mechanism (ESIPT/ICT) fluorescence sensor was responsible for the selective sensing of Zn^{2+} in 20% water acetonitrile. The results showed that the fluorescence sensor can enhance the fluorescence intensity 17-fold. In addition, it responded selectively to Zn^{2+} over other tested metal ions. The sensor developed in this paper contributes to the detection of Zn^{2+}.

4. THE APTAMER-BASED BIOSENSORS

Aptamer-based sensing as one of the possible alternatives to conventional sensing, has high selectivity [57]. In recent years, different researchers have constructed different novel fluorescence sensors and electrochemical sensors, which are referred to as aptamer-based fluorescence sensors and aptamer-based electrochemical sensors. These researchers have applied these special sensors in various fields, such as environmental monitoring, biomedical diagnosis, food safety, and quality control. Aptamer-based electrochemical sensors and fluorescence sensors have important value in the research field.

Food safety is an important part of human life. Due to its good advantages of low cost, high selectivity and sensitivity, sample size, and ease of preparation, fluorescence aptamer sensors exhibit

immense potential for food safety. Electrochemical and fluorescence aptamer sensors have been widely used to detect heavy metal ions and pesticide residues [58]. The following sections outline their application.

4.1 The detection of heavy metal ions

Heavy metal ions, which are of particular relevance to human health, exist in soil and water. Heavy metal residue has become an urgent problem to be solved.

4.1.1 The detection of divalent heavy metal ions

4.1.1.1 Aptamer biosensors for detecting lead ions

Lead, a highly toxic heavy metal iron in our environment, plays an important role in human health [59]. Lead contamination and poisoning problems have persisted to date. The World Health Organization (WHO) claims that the maximum lead concentration is 0.01 mg/L (48 nM) in drinking water. To achieve the detection of lead ions, various types of fluorescence aptamer sensors have been designed.

Huang [60] constructed an ultrasensitive microfluidic electrochemical adapter sensor using nanoporous gold nanolayers as the substrate material for the detection of Pb^{2+}. Aptamer chain S1 was modified on a CeO2@Au NPs composite and was complementary to the aptamer base on the electrode. The target substance, Pb^{2+} was recognized by the aptamer and detected by a change in the electrical signal. Under the optimized experimental conditions, the detection limit of Pb^{2+} was 3.1 pM .

In this research, based on the above description, Zhang [61] used C-PS2.M-DNA-Ag NCs to design a novel fluorescent sensor to selectively detect Pb^{2+}. When in the presence of Pb^{2+}, this sensor could cause the aptamer to form a G-quadruplex, which would leads to the fluorescence. Research has shown that DNA-Ag NCs have good biocompatibility. Additionally, the detection limit was as low as 3.0 nM. This sensor showed potential application for the detection of Pb^{2+} in environmental samples.

In addition to the abovementioned methods, there have been other methods for the detection of Pb^{2+}. Li [62] introduced functional gold-doped carbon dots that could be used not only as a catalyst to amplify the analytical signal but also as a fluorescence probe. In this work, the probe was combined with an aptamer to detect Pb(II). Additionally, a simple paper-based aptasensor by Zahra Khoshbin [63] was presented and had ultrasensitivity for the detection of Pb^{2+}. In this work, Pb^{2+} enhanced the fluorescence allowing for the rapid determination of Pb^{2+} content in tap water, lake water, milk, and human blood serum.

4.1.1.2 Aptamer biosensors for detecting mercury ions

Mercury is a common pollution and is mainly caused by mercury ion pollution. According to Samet Sahin [64], although at low concentrations, mercury ions can cause permanent harm to the nervous

system and lead to DNA damage. The U.S. Environmental Protection Agency (EPA) states that the maximum lead concentration is 2 μg/L (10 nM) in drinking water.

Liu and his team [65] designed an electrochemical adapter sensor to detect Hg^{2+}. The 3' end of the unlabeled hairpin adapter probe HP1 was the recognition site of Hg^{2+}, and the activity of the Hg^{2+}-activated enzyme realized the shearing effect. The clipped adapter chain helper was connected to the complementary chain on the electrode surface, and the quantitative detection of Hg^{2+} was realized according to the electrical signal generated by methylene blue (MB), with a detection limit as low as 227 pM.

In recent years, UCNPs have been an increasingly common fluorescent aptamer sensing materials. To enhance the existing detection approaches, Liu and coworkers [66] developed a turn-on nanosensor based on FRET for detecting Hg^{2+}. FRET occurred because the UCNPs were combined with short-strand aptamer-functionalized gold nanoparticles. In the present Hg^{2+}, the sensor restored quenched fluorescence. This sensor achieved linear detection over range from 0.2-20 μM. In addition, the nanosensor achieved a low detection limit of 60 nM for detecting Hg^{2+} in milk and tap water samples with high selectivity and sensitivity.

Analogous cases, such as a novel label-free fluorescence “turn-on” sensors were studied by Li [67]. The difference between the two reactions lies in the presence or absence of mercury ions. In the absence of Hg^{2+}, MSD (mercury-specific DNA) hybridized with cDNA and could not enhance the fluorescence signal. In the presence of Hg^{2+}, a T-Hg^{2+}-T structure was formed to avoid MSD and cDNA hybridiztion and enhanced.

4.1.1.3 Aptamer biosensors for detecting cadmium ions

Cadmium is one of the most common heavy metals, which exists in soil and water. Cadmium poisoning has become harmful factors to human health. Cadmium ions in the soil are absorbed by crops and enter the human body indirectly. Similarly, cadmium ions in water enter the human body in number of ways, which is harmful to the human health. It can cause serious health problems, for example, some cancers, bone degeneration, and so on. The U.S. Environmental Protection Agency has defined a maximum concentration of 5.0 μg/L for cadmium in drinking water [68].

In 2020, Chang-Seuk Lee [69] designed a labeled electrochemical adapter sensor based on reduced GO for the ultratrace detection of Cd^{2+} ions in water. MB acts as a signalling molecule and influences the changes in electrical signals through the distance of signal molecules on the electrode. The detection platform can achieve a low detection limit (0.65 fM) and is at the leading edge of electrochemical adsorption sensors reported at home and abroad.

Using label-free principles, Zhou [70] designed SYBR green I and conformation switching of an aptamer probe fluorescent aptasensor for the detection of Cd^{2+}. When Cd^{2+} was present, the fluorescence intensity of the system decreased dramatically. The reason for this phenomenon was the presence of Cd^{2+}, and the aptamer preferentially binds to Cd^{2+}, which frees the complementary chain of the aptamer and changes the conformation of the stem ring. Under the optimum experimental parameters, the excellent detection limit was as low as 0.34 μg/L. The fluorescence aptamer sensor showed good

sensitivity and high selectivity, and sample. In the actual sample detection process, the interference caused by pretreatment was reduced.

3.1.2 The detection of multiple metal ions

The development of fluorescent aptamer sensors for highly selective and sensitive detection of multiple metal ions is highly promising but still remains to be a challenge to date [71]. Therefore, simultaneous detection of multiple heavy metal ions is an emphasised direction of study.

A 3D MOF is a common device of fluorescent material for the detection of heavy metal ions in food. MOF has some good advantages such as effective fluorescence quenchers, varied morphologies, good stability, easy controllability, and uniform structures. In 2020, Pavadai Rajaji [72] used a 3D MOF and DNAzyme to design a novel fluorescence biosensor to detect Pb^{2+} and Ag^{2+}. In this search, after adding Pb^{2+} and Ag^{2+}, this fluorescence biosensor produced different effects. The presence of Pb^{2+} effectively enhanced the fluorescence intensity. In contrast, the presence of Ag^{2+} diminished the fluorescence intensity. The working principle of the sensor was as follows, in the presence of Pb^{2+} and Ag^{+}, they have different effects. Pb^{2+} can catalyse the enzymatic cleavage, release interfering substances, and then form g-tetramer-ThT, which can effectively increase the fluorescence intensity. In the presence of Ag^{+}, C-Ag-C is formed, which can reduce the fluorescence signal. This strategy has been successfully applied in practice.

Gui [73] utilized poly(ethylenimine)-functionalized CD_1 and carboxyl-modified CD_2 to prepare dual-emitting carbon dots/carbon dot (CD_1/CD_2). At the same time, this special carbon dot was combined with the aptamer for the detection of Cu^{2+} and Hg^{2+}. The detection limit of Cu^{2+} and Hg^{2+} when using this novel sensor were 0.05 μM and 0.08 μM, respectively. This sensor had high detection recoveries in real water samples and logical fluids.

Taking advantage of the tubular three-dimensional sensing surface and the ordered nanotopography of synthetic materials, Qu [74] designed a DNA-nanostructured microarray (DNM) to synthesize microarray sensors. This novel fluorescence sensor could achieve the detection of multiple heavy metal ions. This paper mainly studied the simultaneous detection of Hg^{2+}, Ag^{+}, and Pb^{2+} and achieved good detection results.

3.2 The detection of pesticide residue

OP pesticides are one of the common pesticides. OP pesticides are prevalent in fruits and vegetables, such as nematocides, insecticides, herbicides, helminthicides, and fungicides, to prevent fruits and vegetables from spoiling during the growing process. OP pesticides are widespread and have a negative impact on human health [75]. Therefore, it is very important for us to study the detection of OP pesticides.

Wang [76] developed a simple two-in-one electrochemical biosensor using dual recognition nuclease (DRAB) for ultrasensitive detection of pesticides and heavy metal ions. Self-enclosed DRABs-containing DNA aptamers and enzyme chains were first activated by insecticide-induced conformational changes, and then specific cleavage of a MB-labeled signaling probe (SP) was achieved in the presence

of target metal ions. The released DRAB insecticide complexes can bind to adjacent SP for another cycle of cutting, resulting in the formation of signal-enhanced DNA nanomachines. The detection limits of chlorpyrifos and Pb^{2+} were 0.178 nM and 0.034 nM, repectively.

As shown in Fig. 6, Qi [77] used exonucase III (Exo III) to assist signal amplification for the sensitive and simultaneous detection of multiple pesticides. Target pesticide recognition of probes drives the production of pesticide-DNA complexes, which hybridize with DNA labeled with electroactive dyes to form double-stranded DNA and then initiate exon-assisted digestion reactions to generate a large number of single nucleotides labeled with electroactive dyes. The detection limits of acetamiprid and propion were 0.0048 nM and 0.0089 nM, respectively.

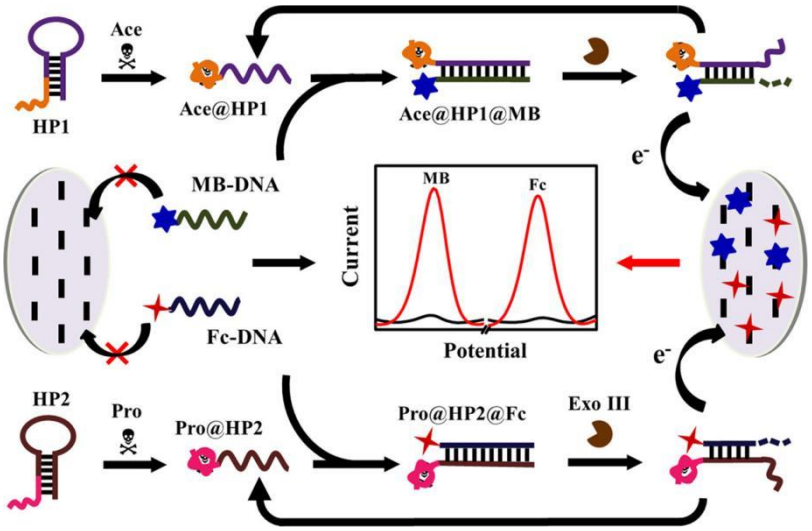

Figure 4. Schematic diagram of the electrochemical principle for the simultaneous detection of two pesticides. [77]. [Reprinted with permission from{Aptamer Recognition-Driven Homogeneous Electrochemical Strategy for Simultaneous Analysis of Multiple Pesticides without Interference of Color and Fluorescence}, Copyright{2020} American Chemical Society.]

Fu [78] first proposed and used one-step electrodeposition technology to fix Apt (Apt) on the sensing interface, and applied this sensor electrochemical aptamer sensors to detect a variety of organophosphorus pesticides. During the preparation of electrodeposition solutions, the NH_2-modified aptamer was connected with GO, providing the basis for immobilization of the aptamer. In addition, copper nanoparticles (CuNPs) were introduced into the apt-GO solution to enhance the conductivity of the electrodeposited film, thus realizing the detection of probromophos, phos mesimibus, thiophos aquifers and omethoate pesticides with detection limits of 0.003 nM, 0.3 nM, 0.03 nM and 0.3 nM, respectively.

In 2020, Li [79] used in aptamer-based fluorescence senor to detect organophosphorus pesticides in food. In this study, they used manganese dioxide (MnO_2) nanosheets were used to fabricate NaY/GdF_4:Yb, Er upconversion nanoparticles, which could be made into a UCNPs-MnO_2 biosensor.

The detection results show that the sensor has good detection performance and a low detection limit. It was an attractive method to detect diazinon in tea products.

Majid Arvand [80] published a new fluorescent sensor that uses quantum dots and graphene oxide. The sensor can detect diazinon with high sensitivity. In the presence of diazinon, the photoluminescence recovered. The primary cause was that graphene oxide (GO) was separated from the aptamer due to its different affinity with the aptamer. The detection limit of the aptasensor was 0.13 nM and could be used to monitor diazinon in environmental and agricultural samples.

The increasing level of pesticides in food and water sources is a threat to the environment and human health. Thus, it is particularly important to develop a fast, sensitive, and selective detection platform [81].

3.3 The detection of biotoxin

There are many kinds of biotoxins in food, which are substances that generally affect human health. Therefore, it is urgent to study the detection methods of food biotoxins [82]. Food biotoxins are present in a wide variety of foodstuffs, including dried fruits, cereals, wine, and beers. Therefore, food biotoxins can enter the human body in various ways and endanger human health [83]. In recent years, with the development of science and technology, detection methods for food biotoxins have endlessly emerged, among which the aptamer sensing technology is fast and efficient. The following are the latest developments in public relations research.

Cai [84] designed a DNA walker and DNA nanoflower using an aptamer chain to detect Staphylococcus aureus. After the Staphylococcus aureus aptamer chain recognition target, the DNA walker was released and the introduction of a specially customized circular DNA and phi29 DNA polymerase initiated a rolling circular amplification (RCA) reaction. The occurrence of RCA provides a locus of action for MB, resulting in a strong signal. Under the optimal conditions, the detection limit of S. aureus was 9 CFU/mL.

Lu's [85] team designed an unlabeled electrochemical adaptor sensor for the detection of oxytetracycline (OTC) in water samples based on Ce-MOF@COF hybrid products. In this study, OTC in milk, urine and wastewater was selected for detection. In addition, the sensor showed good application prospects for the detection of heavy metal particles, antibiotics and tumour markers.

In 2020, Jia [86] composed a novel sensing platform that was combined with an aptamer (marked by Tamra) and a MOF (UiO-66-NH_2). Therefore, the AFB1 content could be analyzed according to the change in the fluorescence signal. The platform could be utilized to detect AFB1 in real samples, for example, rice, milk, and corn.

In 2021, Xiong [87] designed a dual DNA tweezers nanomachine, and one-step simultaneous detection of ochratoxin A (OTA) and AFB1 in food samples could be realized. In the presence of OTA and AFB1, the aptamer bonded to the target substance, and then the dual DNA tweezers nanomachine opened to recover the fluorescence signal. This strategy showed high accuracy and high sensitivity for OTA and AFB1 detection.

3.4 The detection of antibiotics

Antibiotics, which are of particular relevance to broad-spectrum antibacterial activity, exist in multiple foodstuffs [88]. The accumulation of antibiotics in the human body through the food chain can produce some adverse effects. Antibiotics are a class of secondary metabolites that can interfere with the development of other living cells and can be produced and secreted from higher animals, plants, or microorganisms. Accordingly, the detection of antibiotics in food is required. In addition, it limits the use of antibiotics [89].

Wang [90] designed and synthesized a novel covalent organic skeleton (COF) by polycondensation of 1,3,6,8-tetra(4-formylphenyl) pyrene and melamine via imine bonds(Py-M-COF). Py-m-cof not only has an extended π-conjugated framework but also has a large specific surface area, abundant functional groups and a nano sheet structure. Py-m-cof has high carrier mobility, which further improves the strong immobilization of DNA aptamer chains through π-π stacking interaction and electrostatic interactions. Enrofloxacin (ENR) and ampicillin (AMP) were detected by ultrasensitive methods. The detection limits of ENR and AMP using this sensor were 6.07 fg/mL and 0.04 fg/mL, respectively.

Bai [91] captured biotin-labeled aptamer DNA on the electrode surface by hybridization between the probe DNA and aptamer DNA. DsDNA can block the digestion activity of nuclease P1 to single-stranded probe DNA. Then, based on the specific interaction between the double-stranded DNA and the antibody, an anti-double-stranded DNA antibody was further modified on the electrode surface. Due to electrostatic repulsion and steric hindrance, weak electrochemical signals were obtained at the electrode. However, in the presence of sulfadimethoxine, the antibody can interact with aptamer DNA to prevent the formation of double-stranded DNA. According to the change in the electrochemical signal, sulfadimethoxine can be detected, and the detection limit is 0.038 nM.

As shown in Fig. 7, Taghdisi [92] applied a trapezoidal DNA structure on the surface of a gold electrode as a multilayer physical block using the trapezoidal structure of electrostatic repulsion and physical protection, to achieve the ultra-sensitive detection of ampicillin (Ampi). This is because in the presence of Ampi, the trapezoidal DNA structure is decomposed and separated from the electrode surface, resulting in changes in the electrochemical signals. This sensor has a detection limit of 1 pM for Ampi detection.

In order to detect tetracycline (one of the antibiotics, TC) in raw milk, Syed Rahin Ahmed [93] designed an aptamer-based fluorescent sensor to detect TC. This sensor was composed of GQDs and palladium nanoparticles (Pb NPs). This novel sensing strategy provided an efficient way to detect TC and the limit of detection was 45 ng/mL.

Antibiotics exist not only in all kinds of food but also in water. Antibiotics in water enter all kinds of aquatic products and then enter the human body through the food chain, indirectly affecting food safety and harming human health. In 2020, Zhang [94] proposed multivalence aptamer probes to detect multiple antibiotics in different water samples. The fluorescent probe designed in this work not only had a high affinity but could also provide multiple binding sites for the simultaneous detection of multiple target substances. The iterative binding of different binding sites enlarged the recognition effect and greatly improved the responsiveness and sensitivity of the probes.

Table 1 summarizes the different target detection methods used in this work, including the object type, actual sample, signal molecule and detection limit.

Table 1. Summary of recent aptamer-based biosensors.

Target	Real sample	Signal transducer	Linear range	LOD	Reference
Pb^{2+}	water	C-PS2.M-DNA-Ag NCs	5-50 nm	3.0 nM	[61]
	urine	CD_{Au}, TMB	0.005-0.46 μM	0.25 nM	[62]
	tap water, lake water, milk, human blood serum	GO	0.07-20 nM	0.5 pM	[63]
Hg^{2+}	tap water, milk	UCNPs, GNPs	0.2-20 μM	60 nM	[66]
	river water, fish	T-Hg^{2+}-T	10-600 nM	0.24 nM	[67]
Cd^{2+}	river, pond water, tap water, mine pit water	SYBR green I	1.12-224.82 μg/L	0.34 μg/L	[70]
Pb^{2+}, Ag^{+}	tap water, lake water	MnCoPBAs-PDANCs	3-9 nM, 4-20 nM	1.6 nM, 4.2 nM	[72]
Cu^{2+}, Hg^{2+}	water, biological fluids	CD_1/CD_2	0-3.2 μM, 0-8.5 μM	0.05 μM, 0.08 μM	[73]
Hg^{2+}, Ag^{+}, Pb^{2+}	water	DNM	-	10 nM, 10 nM, 20 nM	[74]
Diazinon	tea	NaY/GdF_4:Yb, Er UCNPs	0.1-30 ng/mL	0.1 ng/mL	[79]
	river water, apple fruit, cucumber	Cds QDs/DF2O	1.05-206 nM	0.13 nM	[80]
AFB1	corn, milk, rice	UiO-66-NH_2	0-180 ng/mL	0.35 ng/mL	[86]
AFB1, OTA	corn, peanut, coffee, olive oil, peanut oil	Dual DNA tweezes	-	0.035 ppb, 0.1 ppb	[87]
Tetracyline	raw milk	CQDs	-	45 ng/mL	[93]

Antibiotic	river eel, puffer fish, tap water	Multivalence aptamer probes	-	0.097 nM	[94]

Table 2 summarizes the aptamer sequences required by different targets in this paper. The details are as follows.

Table 2. Sequence of targets aptamers.

Target	Aptamer Sequences	Length (bases)	Refenrence
Pb^{2+}	DNAzyme: 5'-SH-$(T)_7$CATCTCTTCTCCGAGCCGGTCGAAATAGTGAGT-3'	40	[60]
	Substrate strand: 5'-SH-ACTCACTATrAGGAAGAGATG-3'	19	
	5'-GGTTGGTGTGGTTGG-3'	15	[62]
	5'-FAM-GGGTGGGTGGGTGGGT-3'	16	[63]
Hg^{2+}	Primer: 5'-CTTTCTTCTTTGGCCCGG-3'	18	[65]
	HP1: 5'-GTTTGTATGTTGGCCCGGACATACAAACTTTGTTGTTTG-3'	39	
	HP2: 5'-SH-TTACGTATGCCATAGCCAACATACAAAC-MB-3'	28	
	5'-NH_2C_6-CTACAGTTTCACCTTTTCCCCCGTTTTGGTGTTT-3'	34	[66]
	5'-SH-C_6-GAAACTGTAG-3'	10	
	MSD3: 5'-TTTTTTTTTTTTTTTTTTTTTTTTTTCCCCCC-3'	33	[67]
	cDNA3: 5'-GGGGGGAAAAAAAAAAAAAAAAAAAAAAAAAA-3'	33	
Cd^{2+}	5'-GGGGGGGGACTGTTGTGGTATTATTTTTGGTTGTGCAGT-MB-3'	39	[69]
	5'-ACTGCACAACCAAAAATAATACCACAACAGT-3'	31	
	5'-GGGAGGGAACTGTTGTGGTATTATTTTTGGTTGTGCAG TAGGGCGGG-3'	47	[70]
Diazinon	DF20: 5'-NH_2-C_6-ATCCGTCACACCTGCTCTAATATAGAGGTATTGCTCTTGGACAAG GTACAGGGATGGTGTTGGCTCCCGTAT-3'	72	[80]
Tetracycline	5'-CGTACGGAATTCGCTAGCCCCCCGGCAGGCCACGGCTTGGGTTG GTCCCACTGCGCGTGGATCCGAGCTCCACGTG-3'	76	[93]

4. CONCLUSION AND OUTLOOK

In conclusion, aptamer-based biosensors have exhibited potential in the field of rapid safety analysis. However, though relevant works on these sensors have been reported, many problems have emerged. Although aptamers have some advantages, such as high specificity, selectivity, and sensitivity, we found that aptamer-based biosensors still had interference in the process of detecting heavy metal ions. The common interferences when detecting heavy metals are interferences between copper ions and lead ions and cadmium ions, between lead ions and cadmium ions, and between mercury ions and lead ions and cadmium ions. Similarly, there will be interference between objects with similar structures. The key factors that should be considered in the process of sensor design are the background signal in food samples, the stability of fluorescent substances, and so on. In addition, we found that the stability of the fluorescent material also seriously affected the experimental results.

Key research directions include the following: (1) studying the conformation of aptamer recognition elements to improve the stability and repeatability of aptamer screening; (2) an effective preprocessing method needs to be proposed to reduce background interference and the interference in the process of simultaneous detection; (3) finding ways to improve the stability of signaling molecules and fluorescent materials to improve the stability of the sensor; (4) To reduce the impact of multiple pollutants, it is necessary to study the method of simultaneous detection of multiple pollutants; and (5) simplifying the sample pretreatment process and realize the rapid detection of the target object. Multiple studies have found that the combination of aptamer biosensors is also an important future development prospect in the future. Above all, while aptamer-based biosensors are a promising tool that can be applied in environmental detection and food safety analysis, there is still much work that needs to be done. The design of aptamer-based biosensors for applications in food is an important direction.

ACKNOWLEDGEMENTS
The authors gratefully acknowledge the financial support provided all the funds.

FUNDINGS
This work was supported by the Natural Science Foundation of Shandong Province (ZR2018BC055).

Reference

1. N. Duan, H. Wang, Y. Li, S.X. Yang, H.Y. Tian and B.G. Sun, *Coordination Chemistry Reviews*, 427 (2021) 213557.
2. V. Dangi, M. Baral and B.K. Kanungo, *Journal of Fluorescence*, 30 (2020) 1131-1149.
3. M.C. Stoian, I. Mihalache, M. Matache and A. Radoi, *Dyes and Pigments*, 187 (2021) 109144.
4. F. Wang, K.J. Wang, Q. Kong, J. Wang, D.Z. Xi, B.W. Gu, S. Lu, T.W. Wei and X.Q. Chen, *Coordination Chemistry Reviews*, 429 (2021) 213636.
5. X.Y. Zhou, C.C. Wang, L.N. Wu, W. W and S.Q. Liu, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 247 (2021) 119155.
6. J.J. Dong, H.T. Yang, Y. Li, A.R. Liu, W. W and S.Q. Liu, *Analytica Chimica Acta*, 1131 (2020) 102-108.
7. N. Zhao, J.M. Liu, F.E. Yang, S.W. Lv, J. Wang and S. Wang, *ACS Applied Bio Materials*, 4 (2021) 995-1002.

8. F.L. Yue, F.L. Li, Q.Q. Kong, Y.M. Guo and X. Sun, *Science of The Total Environment*, 762 (2020) 143129.
9. L.Y. Wang, X.L. Peng, H.J. Fu, C. Huang, Y.P. Li and Z.M. Liu, *Biosensors and Bioelectronics*, 147 (2020) 111777.
10. H.N. Rubin and M.M. Reynolds, *Inorganic Chemistry*, 58 (2019) 10671-10679.
11. J.J. Peng, J.Y. Li, W. Xu, L. Wang, D.D. Su, C.L. Teoh and Y.T. Chang, *Analytical Chemistry*, 90 (2018) 1628-1634.
12. P.Y. Wang, H.H. Li, M.M. Hassan, Z.M. Guo, Z.Z. Zhang and Q.S. Chen, *Journal of Agricultural and Food Chemistry*, 67 (2019) 4071-4079.
13. A. Khatun, D.K. Panda, N. Sayresmith, M.G. Walter and S. Saha, *Inorganic Chemistry*, 58 (2019) 12707-12715.
14. N. Muhammad, M. Zia-Ul-Haq, A. Ali, S. Naeem, A. Intisar, D.X. Han, H.R. Cui, Y. Zhu, J.L. Zhong, A. Rahman and B.N. Wei, *Arabian Journal of Chemistry*, 14 (2020) 102972.
15. J.S. Liu, H.J. Bao, C.F. Liu, F.F. Wu and F. Gao, *ACS Applied Polymer Materials*, 1 (2019) 3057-3063.
16. H.X. Tan, T. Guo, H.Y. Zhou, H.J. Dai, Y. Yu, H.K. Zhu, H.X. Wang, Y. Fu, Y.H. Zhang and L. Ma, *Analytical and Bioanalytical Chemistry*, 412 (2020) 5627-5635.
17. M.G. Ren, Z.H. Li, B.B. Deng, L. Wang and W.Y. Lin, *Analytical Chemistry*, 91 (2019) 2932-2938.
18. N. Yin, S. Yuan, M. Zhang, J.Y. Wang, Y. Li, Y. Peng, J.L. Bai, B.A. Ning, J. Liang and Z.X. Gao, *Microchimica Acta*, 187 (2020) 21.
19. S. Lavu, B. Mondal and S. Ramlal, *Journal of Fluorescence*, (2021).
20. S.C.G. Kiruba Daniel, A. Kumar, K. Sivasakthi and C.S. Thakur, *Sensors and Actuators B: Chemical*, 290 (2019) 73-78.
21. S. Chung, N.G. Gurudatt, J. Jeon, C. Ban and Y.B. Shim, *Analytical Chemistry*, 93 (2020) 1416-1422.
22. F.Y. Mu, J.Q. He, F. Fan and G.Y. Shi, *Analytica Chimica Acta*, 1105 (2021) 238177.
23. X.Q. Tao, Z.Y. Liao, Y.Q. Zhang, F. Fu, M.Q. Hao, Y. Song and E. Song, *Chinese Chemical Letters*, (2020).
24. R. Khan, T.A. Sherazi, G. Catanante, S. Rasheed, J.L. Marty and A. Hayat, *Food Chemistry*, 312 (2019) 126048.
25. Y.H. He, B.Y. Zhang and Z.F. Fan, *Microchimica Acta*, 185 (2018) 3.
26. M.Y. She, Z.H. Wang, J. Chen, Q.Q. Li, P. Liu, F.L. Chen, S.Y. Zhang and J.L. Li, *Coordination Chemistry Reviews*, 432 (2021) 213712.
27. W.R. Zhong and J.T. Sczepanski, *Acs Sensors*, 4 (2019) 3.
28. Z. Li, S.W. Zhang, T. Yu, Z.M. Dai and Q.S. Wei, *Analytical chemistry*, 91 (2019) 10448-10457.
29. J.D. Sun, Y. Gan, T. Liang, S.Q. Zhou, X.Y. Wang, H. Wan and P. Wang, *Current Opinion in Electrochemistry*, 17 (2019) 23-29.
30. M.Q. Hong, M.Y. Wang, J. Wang, X.Q. Xu and Z.Y. Lin, *Biosensors and Bioelectronics*, 94 (2017) 19-23.
31. L.S. Lu, B. Liu, J. H. Leng, X. Ma and H.H. Peng, *Analytical and Bioanalytical Chemistry*, 412 (2020) 7169-7178.
32. M.N. Nan, Y. Bi, H.L. Xue, H.T. Long, S.L. Xue, L.M. Pu and D. Prusky, *Food Chemistry*, 337 (2021) 127761.
33. Y.L. Zhang, C.W. Li, L.F. Zhou, Z.P. Chen and C.Q. Yi, *Microchimica Acta*, 187 (2020) 437-448.
34. Srinivasan, V. Ranganathan, M.C. Derosa and B.M. Murari, *Analytical & Bioanalytical Chemistry*, 411 (2019) 1319-1330.
35. K. Ma, F.L. Zhang, N.M. Sayyadi, W.J. Chen, A.G. Anwer, A. Care, B. Xu, W.J. Tian, E.M. Goldys and G.Z. Liu, *Acs Sensors*, 3 (2018) 320-326.
36. B.Z. Zhang and C.Y.Wei, *Talanta*, 182 (2018) 125-130.

37. V.D. Dang, A.B. Ganganboina and R.A.Doong, *ACS Applied Materials and Interfaces*, 12 (2020)3 2247-32258.
38. A.Thakur and P. Devi, *Transactions of Indian National Academy of Engineering*, (2021).
39. Y.Y. Wang, W.T. Li, X.T. Hu, X.N. Zhang, X.W. Huang, Z.H. Li, M.Y. Li, X.B. Zou and J.Y. Shi, *Food Chemistry*, (2021) 129352.
40. J. An, R.B. Chen, M.Z. Chen Y.Q. Hu, Y. Lyu and Y.F. Liu, *Sensors and Actuators B Chemical*, 329 (2020) 129097.
41. T.G. Zhang, L.L. Zhu and W.Y. Lin, *Dyes and Pigments*, 188 (2021) 109177.
42. D.H. Li, J. Ma, H.L. Wang, L. Liu and H.G. Yang, *Journal of Materials Science*, 2 (2021) 56.
43. Z.S. Pehlivan, M. Torabfam, H. Kurt, C.O. Yang and N. Hidebrandt, *Microchimica Acta*, 186 (2019) 573.
44. A.B. Pebdeni, M. Hosseini and M.R. Ganjali, *Food Analytical Methods*, 13 (2020) 5.
45. A. Afzalinia and M. Mirzaee, *ACS Applied Materials and Interfaces*, 12 (2020) 14.
46. Q.S. Chen, R. Sheng, P.Y. Wang, Q. Ouyang, A.C. Wang, S. Ali, M. Zareef, M. M. Hassan, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 241 (2020) 118654.
47. S. Gao, L. Wang, Z.J. Zhang, R. Li, Q. Wang, G.J. Wang, H. Wei and X. Ouyang, *Chemical Engineering Journal Advances*, 5 (2021) 100069.
48. D.C. Magri, *Coordination Chemistry Reviews*, 426 (2021) 213598.
49. M.S. Arabi, C., Karami, M. A. Taher and E. Ahmadi, *JBIC Journal of Biological Inorganic Chemistry*, 25 (2020) 1.
50. S.B. Chen, S.N. Zheng, S.J. Jiang, H.Y. Guo and F.F. Yang, *Analytical and Bioanalytical Chemistry*, (2021) 1-12.
51. X.L. Lu and W. He, *Chinese Journal of Analytical Chemistry*, 49 (2021) 2.
52. Y.H. Yan, X.L. Cui, Z.Y. Li, M.M. Ding, Q.L. Che, J.Y. Miao, B.X. Zhao and Z.M. Lin, *Analytica Chimica Acta*, 1137 (2020) 47-55.
53. J.Q. Sun, Y.F. Li, S. Shen, Q.M. Yan, G.M. Xia and H.M. Wang, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 228 (2020) 117590.
54. D.C. Magri, *Coordination Chemistry Reviews*, 426 (2021) 213598.
55. L.B. Yu, X.L. Hao, C. Zhang, T.F. He and A.M. Ren, *Journal of Photochemistry and Photobiology A: Chemistry*, 397 (2020) 112525.
56. B. Mahantesh, N. Ganesh, P., Shivaraj, P. Kadolkar, K. Gudasi and S. Inamdar, *Journal of Photochemistry and Photobiology A: Chemistry,* 390 (2020) 112298.
57. S. Ansari and S. Masoum, *Talanta*, 223 (2021) 121411.
58. X.L. Luo, Y. Han, X.M. Chen, W.Z. Tang, T.L. Yue and Z.H. Li, *Trends in Food Science and Technology*, 95 (2020) 149-161.
59. Y.J. Yang, W.X. Li and J.W. Liu, *Analytica Chimica Acta*, 1147 (2021) 124-143.
60. Y.Z. Huang, Y.K. Han, Y.K. Gao, J.W. Gao, H. Ji, Q.H. He, J.B. Tu, G.Q. Xu, Y, Zhang and L. Han, *Electrochimica Acta*, 373 (2021) 137921.
61. B.Z. Zhang and C.Y. Wei, *Talanta*, 182(2018) 125-130.
62. D. Li, X.Yuan, C.N. Li, Y.H. Luo and Z.L. Jiang, *Journal of Luminescence*, 221 (2020) 117056.
63. Z. Khoshbin, M. R. Bozorgmehr, M. Izadyar, A. Verdian and M.R. Bozorgmehr, *Analytica Chimica Acta*, 1071 (2019) 70-77.
64. S. Samet, M.O. Caglayan and Z. Ustundag, *Talanta*, 220 (2020) 121437.
65. X.L. Song, Y. Wang, S. Liu, X. Zhang, H.W. Wang, J.F. Wang and J.D. Huang, *Royal Society of Chemistry*, 143 (2018) 5771.
66. Y. Liu, Q. Ouyang, H.H. Li, M. Chen, Z.Z. Zhang and Q.S. Chen, *Journal of Agricultural and Food Chemistry*, 66 (2018) 24.
67. Z.H. Li, H.J. Sun, X.Y. Ma, R.F. Su, R. Sun and C.Y. Yang, *Analytica Chimica Acta*, 1099 (2020) 136-144.

68. M.Z. Liu, W. Zhou, H. Tavakoli, C, Bautista, J.F. Xia, Z.H. Wang and X.J. Li, *Biosensors and Bioelectronics*, 176 (2021) 112947.
69. C.S. Lee, S.H. Yu and T.H. Kim, *Microchemical Journal*, 159 (2020) 105372.
70. B. Zhou, X.Y. Yang, Y.S. Wang, J.C. Yi, Z. Zhen, H. Zhang, Y.T. Chen, X.J. Hu and Q.L. Suo, *Microchemical Journal*, 144 (2019) 377-382.
71. R.R. Gao, W. Zhao, Q. Qiu, A. Xie, S.Y. Cheng, Y.Z. Jiao, X.H. Pan and W. Dong, *Sensors and Actuators B Chemical*, 320 (2020) 128448.
72. Pavadai Rajaji and Perumal Panneerselvam, *ACS Omega*, 5 (2020) 39.
73. R.J. Gui, J. Hui, Y.F. Wang and J. Sun, *Sensors and Actuators B: Chemical*, 245 (2017) 386-394.
74. X.M. Qu, F. Yang, H. Chen, J. Li, H.B. Zhang, G.J. Zhang, L. Li, L.H. Wang, S.P. Song, Y. Tian and H. Pei, *Acs Applied Materials and Interfaces*, 9 (2017) 16026-16034.
75. C.S. Pundir, M. Ashish and Preety, *Biosensors and Bioelectronics*, 140 (2019) 111348-111348.
76. W.R. Wang, Y.C. Xu, N. Cheng, Y.X. Xie, K.L. Huang and W.T. Xu, *Sensors and Actuators B: Chemical*, 321 (2020) 128598.
77. H.J. Qi, H.Y. Li and F. Li, *Analytical Chemistry*, 01 (2021) 93.
78. J.Y. Fu, X.S. An, Y. Yao, Y.M. Guo and X. Sun, *Sensors and Actuators B: Chemical*, 287 (2019) 503-509.
79. H.H. Li, S. Ali, W.Y.Wei, Y. Xu, H.W. Lu, M.M. Hassan, X.Y. Wu, M. Zuo, Q. Ouyang and Q.S. Chen, *Microchemical Journal*, 159 (2020) 105462.
80. M. Arvand, A.A. Mirroshandel, *Food Chemistry*, 280 (2019) 115-122.
81. V. Kumar, K. Vaid, S.A. Bansal and K.H. Kim, *Biosensors and Bioelectronics*, 165 (2020) 112382.
82. A.V. Samokhvalov, I.V. Safenkova, S.A. Eremin, A.V. Zherdev and B.B. Dzantiev, *Analytical Chemistry*, 90 (2018) 9189-9198.
83. K.L. Fadock and R.A. Manderville, *ACS Omega*, 2 (2017) 8.
84. R.F. Cai, S.X. Zhang, L. Chen, M.L. Li, Y.T. Zhang and N.D. Zhou, *ACS Applied Materials and Interfaces*, 13 (2021) 4905-4914.
85. N. Zhou, Y.S. Ma, B. Hu, L.H. He, S.J. Wang, Z.H. Zhang and S.Y. Lu, *Biosensors and Bioelectronics*, 127 (2019) 92-100.
86. Y.M. Jia, G.H. Zhou, X.D. Wang, Y.Z. Zhang, Z.G. Li, P.L. Liu, B. Yu and J. Zhang, *Talanta*, 219 (2020) 121342.
87. Z.W. Xiong, Q. Wang, Y.J. Xie, N. Ling, W. Yun and L.Z. Yang, *Food Chemistry*, 338 (2021) 338:128122.
88. J. Li, .F. Yu, Y.N. Wu, Y.J. Zhu, J.J. Xu, Y. Wang, H.T. Wang, M.T. Guo and F.T. Li, *Environment International*, 125 (2019) 135-141.
89. F.L. Yue, F.L. Li, Q.Q. Kong, Y.M. Guo and X. Sun, *Science of The Total Environment*, 762 (2021) 143129.
90. M.H. Wang, M.Y. Hu, J.M. Liu, C.P. Guo, D.L. Peng, Q.J. Jia, L.H. He, Z.H. Zhang and M. Du, *Biosensors and Bioelectronics*, 132 (2019) 8-16.
91. Z.H. Bai, Y. Chen, F. Li, Y.L. Zhou, H.S. Yin and S.Y. Ai, *Talanta*, 204 (2019) 409-414.
92. S.M. Taghdisi, N. M. Danesh, M.A. Nameghi, M. Ranmezani, M. Alibolandi and K. Abnous, *Biosensors and Bioelectronics*, 133 (2019) 230-235.
93. S.R. Ahmed, S. Kumar, G.A. Ortega, S. Srinivasan and A.R. Rajabzadeh, *Food Chemistry*, 346 (2021) 128893.
94. Y. Zhang, Y. Hu, S. Deng, Z.L. Yuan, C.H. Li, Y.H. Lu, Q. He and R.J. Deng, *Journal of Agricultural and Food Chemistry*, 68 (2020) 2554-2561.