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Ensuring food safety using aptamer based assays: Electroanalytical approach

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ABSTRACT

Aptamers, are being increasingly employed as favorable receptors for constructing highly sensitive biosensors, for their remarkable affinities towards certain targets including a wide scope of biological or chemical substances, and their superiority over other biologic receptors. The selectivity and affinity of the aptamers have been integrated with the wise design of the assay, applying suitable modifications, such as nanomaterials on the electrode surface, employing oligonucleotide-specific amplification strategies or, their combinations. After successful performance of the electrochemical aptasensors for biomedical applications, the food sector with its direct implication for human health, which demands rapid and sensitive and economic analytical solutions for determination of health threatening contaminants in all stages of production process, is the next field of research for developing efficient electrochemical aptasensors. The aim of this review is to categorize and introduce food hazards and summarize the recent electrochemical aptasensors that have been developed to address these contaminants.

1. Introduction

Foodborne diseases are increasingly treating worldwide because of industrial globalization and an ever-increasing urban population that has resulted in a massive demand for the food supply and have led to compromise on food quality. To prevent this, detection of possible contaminants through routine controls in every stage of the food supply is highly critical. In this context, all kinds of food safety issues, including those originated from physical, biological and chemical factors related to hygiene issues, as well as illegal adulterations and unauthorized additives, needs to be carefully monitored by means of highly sensitive analytical devices that are more practical than precise liquid or gas chromatography hyphenated with mass spectrometry, which are laboratory controlled, cumbersome, complex, costly and require well trained operators [1]. Among all the instrumental and manual laboratory-based analytical approaches, biosensors are the best candidates as sensitive technologies that can be substituted for traditional approaches, having better sensitivity and selectivity, especially when integrated with advances in nanotechnology and unique achievements of biotechnology.

Since the first introduction of the exponential enrichment (SELEX) procedure in 1990, aptamers have emerged as high-affinity oligonucleotides with many unique features and have been combined with many separations and analytical devices and been employed in various areas of medical and pharmaceutical basic researches, drug development, disease diagnosis, and delivery of therapeutics [2]. High selective binding aptamers as single stranded oligonucleotides with a remarkable role in biotechnology can be either DNA or RNA based, which are isolated from a huge library of randomised oligonucleotides during consecutive cycles of incubation with the target, partitioning and amplification [3]. Aptamers have proved high potential to be replaced for antibodies in biosensor development as the biorecognition elements, because of offering several advantages over antibodies, such as better stability, simple

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storage, in vitro synthesis, low cost, easy modification and remarkably high affinity. Meanwhile, their smaller size makes them preferential for miniaturised systems as they can form a dense surface coverage of monolayers, which are also capable of being recycled upon breaking the aptamer-target complex, which is not normally possible with antibodies [4]. In addition, many food contaminants include substances that do not induce antibody generation, here aptamers remain to be an almost ideal option as highly selective, resistant and cost-effective option for biosensing [5]. Aptamers can recognise a vast variety of targets owing to their three-dimensional folding and adaptive conformational switching and being flexible for different modifications. Accordingly, it has gained extensive interest for food safety monitoring, and numerous aptasensors based on different transduction pathways have been designed in last decades for determination of the wide scope of biological and chemical substances. Recently, remarkable attempts have been made to improve several aspects of them, including selectivity (blended-SELEX, counter-SELEX, and negative-SELEX) and the selection time during SELEX procedure (automated-SELEX) [6].

Considering the huge number of reports on aptasensors with a focus on food control, the great potential of aptasensors as versatile, sensitive and selective analytical devices for prevention of health hazards is evident. Nanomaterials have added excellent features for development of highly sensitive biosensors and almost every reported recent biosensor have benefited from at least one of the advantages offered by nanomaterials as an electrode material, labels attached to biomolecules, biomolecule carriers, etc [7a–w]. Nanomaterials have been incorporated in the construction of biosensors for food quality assessments commonly aiming to amplify the response signal and as the immobilisation platform for the biomolecules. Especially electrochemical biosensors, which are known to be advantageous because of low cost, easy to fabricate and being more feasible to be miniaturized, can be promoted by incorporating nanomaterials to find wide applications in food sector including food processing, storage, and distribution, in particular for food control. Food control consists of different aspects including testing safety markers, predicting shelf-life and fermentation, detecting the adulterations and process monitoring [8]. Herein, the scope of the review is confined to the recent electrochemical aptasensors that have been fabricated for determination of pathogens, additives and harmful chemicals. These substances can be generally classified into toxins, growth promoters (metabolic modulators and antibiotics), food allergens, microbial pathogens and other frequently encountered food contaminants (bisphenol, estradiol, chloramphenicol, etc.).

Some recent papers have attempted to summarise aptasensors that have been developed for food safety monitoring along with introducing the advancements in this field [9,10] with main focus on aptamer technology, independent of the employed analytical device or the transduction technique, in the case of biosensors. Some other studies have been devoted to summarising the aptasensors fabricated for just a specific categories of food contaminants, such as allergens [11], microbial and viral contaminants [12] and toxins [13]. This comprehensive review discusses all the main classes of food contaminants and summarizes all the recent reports of aptasensors for food analysis but with focus on electrochemical transduction techniques.

2. Characteristics of key food contaminants

2.1. Growth promoting feed additives

While veterinary drugs, including antimicrobials, hormones, and growth promoters play an essential role in the treatment of animal diseases and increase the efficacy of animal-derived food, the residues of veterinary drugs, which retain in these foodstuffs, pose serious adverse effects to human health. Hence, several limitations have been announced in some countries and prohibited in many others [14a]. Several cases of pathogen resistance toward antibiotics in humans because of consuming meats that have been treated with antibiotics during livestock breeding and heart arrhythmia and stress caused by β-agonists are some health-threatening effects of feed additives [14b].

2.2. β-Agonists

One of the well-known controversial groups of growth promoters is β-agonists. They are comprised of phenylethanolamines with different functional groups on the aromatic ring, such as phenol, aniline, or resorcinol group [15a]. This group of growth-promoting agents demonstrate anabolic features because of contributing to skeletal muscle development and decrease in the fat deposition, which explains why they have been widely used as livestock feed additives. β-Agonists are typically prescribed for the treatment of respiratory diseases that act upon attaching to the β2 receptor, relieving the smooth muscle of respiratory tract, however, the misuse of these substances have brought strict regulations for their consumption in numerous countries such as European nation, China, Japan, etc. [15b].

2.3. Antimicrobials

Applications of antibiotics in veterinary medicine consists of a therapeutic applications for curing infected animals, which is administered in a high dosage and short time period, the prevention of infection in moderate to high dosage of antibiotics, and promotion of growth in minimal antibiotic levels over an extended time period [16a]. Mechanisms engaged in antibiotic-mediated growth enhancement in animals fed with antibiotics could be through (i) repression of subclinical infections, (ii) decreasing microbial metabolites, which are growth-depressing, (ii) preventing ingestion of nutrients by microbial agents, and (iv) accelerating nutrients uptake across the thinner intestinal wall [16b]. Although adding non-therapeutic levels of antimicrobial growth promoters in livestock feed, which include different classes of antibiotics, have widely contributed to animal health and projected in remarkable increase in livestock production, these substances have been banned in European Union (EU) because of several evidences of pathogenic antibiotic resistance in human and ongoing public concerns on this issue [16c].

2.4. Food allergens

Food allergens are another class of food ingredients, either proteins or glycoproteins that can potentially stimulate immune responses, which can be moderate to severe and therefore have caused global health concerns. These substances are often present in trace levels, which make their determination highly critical. Due to health hazards of allergens for sensitised individuals, in several countries, there have been legislations on the declaration of potentially allergen ingredients in food labelling. Also, the risk of cross-contamination during food process and storage is another issue, which dictates careful and precise determination of allergens [17a]. Allergens can be classified into IgE-mediated allergens, which can cause immediate immunologic responses through administrating allergens in oral or inhaled form, the cell-mediated allergens, which cause delayed responses, and mixed allergens (cell and IgE-mediated); each demonstrate different symptoms from digestive, respiratory and dermal to more extreme, life-threatening symptoms [17b]. Food ingredients that are usually regarded as an

allergen in European nations are eggs, milk, peanuts, nuts, gluten, lupin, soybeans, celery, mustard, sesame seeds, fish, crustaceans, molluscs and sulphites [17c].

2.5. Microbial pathogens

As foodborne diseases originated from microbial pathogens are one of the major causes of death in several countries, the rapid and accurate detection of a specific strain of bacteria, especially in very low concentrations is vital for early diagnosis and effective treatment [18a]. The facts and real dimensions of food health challenge can be understood by considering statistics of food poisoning in the year 2000 caused by 5 types of bacteria in USA, which came at a cost of $6.9 million for medical costs, decrease in productivity and premature child death incidents. This number illustrates the possible outcome of food poisoning outbreaks in developing and underdevelopment countries with insufficient food control and health conditions [18b]. *Escherichia coli* and especially its dangerous type referred to as enterohemorrhagic *E. coli* O157: H7 is one of the main causes of foodborne outbreaks, which leads to several serious health hazards, such as the intestinal damage, anemia, abdominal cramps with bloody diarrhea, hemolytic uremic syndrome and thrombotic thrombocytopenic purpura [18c]. The other prominent pathogens responsible for food outbreaks include Salmonella, campylobacter and *L. monocytogenes*, the food-borne viral pathogens, such as SARS coronavirus and the avian influenza viruses and food-borne parasites, including parasitic worms and numerous types of protozoa [18d].

2.6. Toxins

Pathogenic bacteria are responsible for producing toxins in food products contaminated with these microorganisms, which pose a high risk for human health. Endotoxins are a class of toxins that are expressed on the outer surface of gram-negative bacteria, while exotoxins are extracellular toxins secreted by bacteria to the surrounding, which induces varieties of host responses and is the primary cause of the most foodborne diseases. A popular example for exotoxins is botulinum neurotoxins produced by Clostridia botulinum [9]. Mycotoxins are secondary metabolites produced by filamentous fungi, which are consist of 500 different subclasses and are usually arisen by inappropriate storage of foodstuffs, mainly crops and animal feed. The other classes of toxins are phycotoxins, which are byproducts of toxicogenic microalgae and are mainly found in seafood, and also cyanotoxins that are produced by cyanobacteria. The popular class of cyanotoxins is microcystin-LR [19].

2.7. Other food contaminants

Chemical environmental and food contaminants, especially endocrine disrupting compounds, such as polychlorinated biphenyls, bisphenol A, 4-n-nonylphenol and hormones, such as 17β-estradiol, due to their persistence in environment, bioaccumulation and entering higher levels of the food chain can lead to adverse health issues [20a–d]. These compounds are usually by-products of industries, for instance, 4-n-nonylphenol is widely used as surfactants and bisphenol A, has wide applications in the plastic industry and as dental sealants, which can be transferred to human body via plastic baby bottles while feeding infants, dental sealants of patients through saliva and by industrial waste directly into fresh waters [20e].

3. Electrochemical platforms for aptasensing

Since the first report on electrochemical aptasensor in 2004, which was thrombin-sensing amperometric sandwich-based aptasensor with glucose dehydrogenase as signalling labels [21a], electrochemical aptasensing has been rapidly growing with a vast number of publication that covers several fields of science, such as medical diagnosis, environmental and food control, forensics, etc. Electrochemical transduction system offers varieties of advantages for aptasensing, such as miniaturised, relatively compact, easy to manage, and economically feasible instrumentation, which yields rapid analytical responses and high sensitivity with very low limits of detections making them highly desirable for on-site analysis [21b].

The majority of the electrochemical aptasensors reported so far are based on applying varieties of voltammetry techniques, all of which have been categorised as a subclass of amperometry. The other commonly applied techniques are potentiometry, electrochemical impedance spectroscopy (EIS), field effect transistors (FET) and in few cases, electrochemical quartz crystal microbalance [21c]. Exploiting the structural flexibility of aptamers, several sensing schemes have been designed to fulfil special analytical needs depending on the analyte type and its concentration, such as direct assay, sandwich assay, aptamer conformational switch, target molecules displacement, etc. [21d]. Common practices in developing electrochemical aptasensor assays include incorporating the electroactive substances as redox labels either by covalent or non-covalent binding into the aptamer. The aptasensors with non-covalently incorporated electroactive substances, which are denoted as label-free formats, include intercalation of the electroactive substance by electrostatic interaction with nucleic acids [21e]. As an alternative to labels, usually, a redox indicator is incorporated into the detection medium as a mediator, which undergoes redox reaction and can be traced by considering its redox peaks in the presence of different concentrations of analyte and in its absence. While labelling enables the ultrasensitive detection of a single macromolecule, it is associated with alterations in the binding affinities and conformational changes of the biomolecules and affects the kinetics of the biochemical reagents, therefore, developing label-free electrochemical aptasensors has attracted immense attention, especially the nanoparticle-modified label-free electrochemical assays [21f]. One classic approach is to design label and mediator-free sensing scheme using conductive and electrochemically active substrate, in which the change in surface characteristics, such as dielectric properties of electrode surface in FET, is directly measured and attributed to analyte concentration [21g].

4. Applications for determination of food contaminants

4.1. Detection of growth promoting feed additives

4.1.1. β-Agonists

There is a handful of literature regarding electrochemical aptasensors that have been developed for the determination of β-agonists. The majority of recent investigations for determination of β-agonists are devoted to combinative immunoassays, such as lateral flow immunochromatography [22a–e] and optical immunosensors, especially plasmonic immunosensors that have proved remarkable progress for determination of beta agonists in recent years [22f–k]. However, considering the excellent quantitative results obtained by electrochemical approaches and previously described advantages of aptamers over antibodies, electrochemical aptasensors benefited with nanomaterials are highly promising for determination of this class of growth promoters. Yang and coworkers [22l]. reported electrochemical ractopamine (RAC) aptasensor based on gold nanoparticles/polydimethyl diallyl ammonium chloride-graphene composite (AuNPs/PDDA-GN), which employed an as highly conductive substrate for immobilization of RAC -specific aptamer. The graphene surface and gold NPs highly enhanced the electroactivity of the

surface and promoted electron transfer between ferricyanide/ferrocyanide redox pair (mediator). The limit of detection (LOD) as low as 5.0×10^{-13} mol/L for RAC. HCl was achieved according to calibration curves obtained by analysing differential pulse voltammetry assay. In a different strategy, Sheng et al. [22m] designed ultrasensitive RAC aptasensor based on enzyme-free hairpin DNA cascade amplifier and dsDNA-templated synthesis of the CuNPs (dsDNA/CuNPs). Two non-complementary hairpins (HA1, HA2) and RAC aptamer, which was hybridized with a triggering oligonucleotide sequence, were fabricated and upon introducing RAC, the aptamer sequence was detached from the trigger, leading to HA1 hybridization with trigger and then with HA2. Consequently, the generated dsDNA structure trapped Cu in the presence of sodium ascorbate, which resulted in the CuNP formation and the highly enhanced electrical signal.

According to the base structure of the beta agonists, which are all comprised of phenylethanolamines (PHL) with different functional groups on the aromatic ring, Chen et al. [22n] isolated 22 pair PHL aptamer with 3.34×10^{-5} mol L^{-1} dissociation constant. The developed label-free electrochemical aptasensor exhibited high sensitivity towards 5 types of beta agonists (phenylethanolamine, clenbuterol, RAC, salbutamol and procaterol) with detection limits of 1.0 pg/mL, 0.35 pg/mL, 0.04 ng/mL, 0.53 pg/mL and 1.73 pg/mL, respectively.

4.1.2. Antibiotics

In recent years, there has been an intensive study on developing electrochemical aptasensors for detection of antimicrobials in food products and veterinary residues. Although promising, commercialization of these aptasensors for analysing real food and feed samples is an issue [23a]. Specific aptamers for varieties of prominent antibiotics, such as penicillin [23b], chloramphenicol [23c], tetracycline [23d], kanamycin (KAN) [23e], streptomycin [23f], malachite green [23g], etc. are available.

Tetracyclines (TCs) are the widely employed antibiotics for human and animal treatment and have been widely investigated by aptasensors in veterinary residues. The popular members of TCs are oxytetracycline (OTC), tetracycline (TC), chlortetracycline and doxycycline, with wide applications in food-producing animals. TC the prominent type of TCs, is absorbed in small amount through the animal intestinal tract and mainly remains in veterinary wastes and can accumulate in the environment [23h,i]. It has demonstrated several adverse effects, such as the antibiotic resistance, liver damage, allergic reactions in hypersensitive individuals, change in gut flora, vision problems, and tooth discoloration in infants [23j]. Milk samples are commonly investigated for TC levels using aptasensors, while honey as possible food matrix has also been analysed for TC, as it is often added in the production process of honey to treat bacterial bee brood infection in apiculture [23k].

Varieties of nanomaterial modifications have been applied to the solid electrode surface for improving electrocatalytic properties of the substrate and improving the aptamer immobilisation leading to lower detection limits. In a study toward determination of TC, multi-walled carbon nanotubes (MWCNTs) with functional carboxyl groups were applied on glassy carbon electrode (GCE) as a platform to immobilise NH2-modified TC-aptamer and to establish high conductivity as nanowire between the electrode and electrolyte solution [23d]. Shen et al. used MWCNTs in chitosan (CS) solution and Prussian blue (PB)-graphene nanocomposite/CS as successive layers on GCE and immobilised TC-aptamer on the modified electrode surface via glutaraldehyde. The LOD as low as 0.56×10^{-11} M was achieved by analysing DPV results of different TC concentrations. In a similar study, GCE was modified with PB-chitosan-glutaraldehyde and colloidal gold NPs layers for TC-aptamer immobilisation. The detection limit of 3.2×10^{-10} M was achieved by the proposed electrochemical aptasensor [23l].

Xu et al. [23m] used antimony tin oxide nanoparticle-chitosan (nano ATOs-Cs) platform to combine electrical conductivity of nano-antimony tin oxide (nano ATOs) achieved by incorporating antimony to high resistant TO, and the good immobilisation ability of the CS. The electrochemical TC aptasensor demonstrated low detection limit of 3.0×10^{-9} g/mL and performed satisfactorily in TC-spiked milk samples. In another study, a composite of reduced graphene oxide (RGO), magnetite (Fe_3O_4) nanoparticles and sodium alginate composite was constructed for TC aptasensing. The RGO and Fe_3O_4 improved the limitations and enhanced the advantages of each other leading to significantly amplified current responses upon TC binding to surface immobilised aptamer in the presence of thionine redox mediator [23i].

In a very recent report, Kesavan et al. developed an electrochemical aptasensor with GCE modified with polymelamine (p-Mel) film on electrochemically reduced graphene oxide (ERGO) by the potentiodynamic method and the sensor response for TC in human urine samples was analysed to evaluate the performance of aptasensor in the presence of uric acid interference. The LOQ of 2.2×10^{-6} M resulted in 50 fold excess of uric acid concentration [23j]. The conductivity and electrochemical response of the aptasensor and sensitivity could be further improved by incorporating nanoparticles onto the electrode surface. As can be estimated, amplification of the electrode response and achieving lower detection limit without employing nanomaterials, require designing aptameric assays that are more complex with longer experimental time. In a recent paper, Taghdisi et al. [23n] developed M-shaped electrochemical aptasensor based on TC-aptamer, 3 complementary oligonucleotides and exonuclease I (ExoI). Upon introducing the target, M-shaped structure disassembled because of the aptamer affinity toward target and its detachment from complementary sequences, followed by adding EXOI, which selectively degraded the remaining sequences allowing ferrocyanide redox probe to reach the electrode surface. The reported aptasensor demonstrated high sensitivity of 450 pM and good performance in milk and serum samples with LODs of 0.74 nM and 0.71 nM, respectively. Another exonuclease-assisted aptamer assay was reported by Yan et al. [23o], which was the multiplex CAP and OTC assay, based on metal ion signal tags encoded by magnetic hollow porous nanoparticles (MHPs), selective aptamers of the antibiotics, complementary sequences of each aptamer (S3, S4) and exonuclease I (ExoI). In the presence of target antibiotics, aptamers were detached from complementary sequences, captured the target and later selectively degraded by EXOI, leading to target release. After adding the signal tags bearing complementary strands (S1, S2), the remained sequences (S3, S4) were hybridised by signal tags, which yielded amplified current signals that were recorded by applying SWV. There are some recent reports on applying the exonuclease-assisted targets recycling amplification strategy in electrochemical aptasensors for ultrasensitive detection of other types of antibiotics, such as ampicillin [23p], oxytetracycline and kanamycin [23q].

There has been a major focus on developing voltammetric TC aptasensors, however, recent studies with impedance spectroscopy transduction has also proved the powerful analytical capability of this platform with label-free, simple scheme and high sensitivity for detecting TC in real samples [23q,r]. Meanwhile, it is less destructive towards protein layers applied on the electrode surface compared to direct methods of voltammetry and has been widely employed for studying the electrochemical behaviours of the sensor through monitoring some processes occurring in the cell, such as capacitive, inductive, and diffusion processes [23s]. Fig. 1 depicts an illustration of the electrochemical aptasensing assay for multiple antibiotic detections using varieties of quantum dot tags.

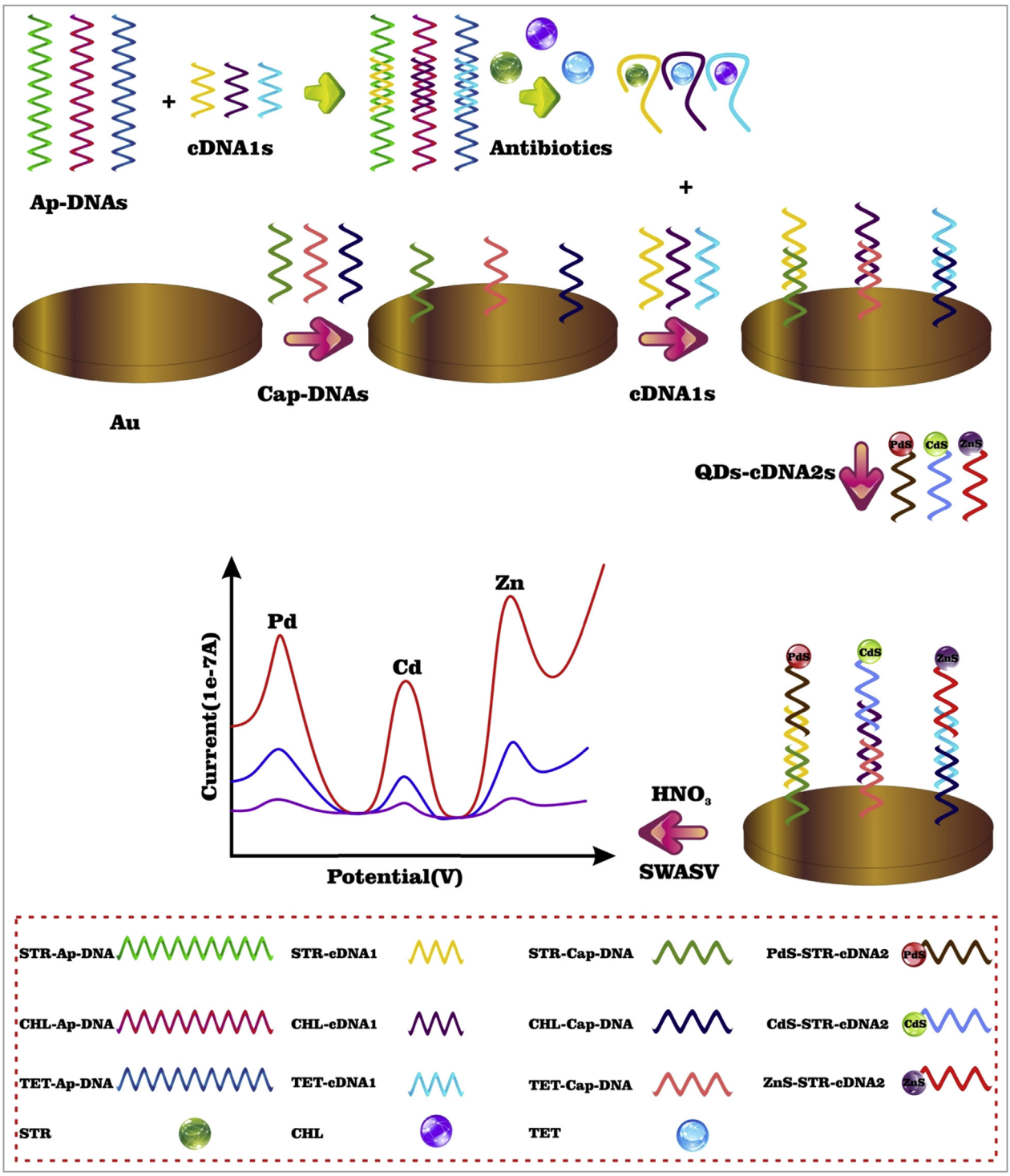

Fig. 1. Schematic representation of aptamer assays including different antibiotic specific aptamers with the relevant quantum dot tagged complementary DNAs for simultaneous electrochemical detection of multiple antibiotics. Re-drawing by Corel Draw 6.0 software.

Recently, several other types of antimicrobials have been investigated by electrochemical aptasensors (Table 1) for the purpose of food control.

4.1.3. Detection of allergens

First attempts toward quantitation of lysozyme (LYS) as one of the major food allergens by electrochemical aptasensor goes back to more than a decade ago, in-line with growing reports of successful aptasensors toward small protein determination [25a–c]. Lysozyme is an abundant enzyme found in body fluids of mammals (0.5–2.0 mg/ml at blood) and also egg white (3.5%), which plays a natural antibacterial role by degrading glycoprotein wall of gram-positive bacteria through catalyzing the cleavage of its acetal group [25d,e]. LYS has application in food industry as a preservative, in food packaging to inhibit microbial growth [25f] and in the production process of foodstuffs, such as ripened

Table 1
Recently developed electrochemical aptasensors for antibiotic determination.

Antibiotic	Electrode details	Electrochemical transduction	Analyzed samples	Linear range	LOD	Ref.
Oxytetracycline	Gold electrode functionalized with a dsDNA monolayer (formed from ferrocene (Fc)-labeled DNA-1 and DNA-2, i.e. the OTC aptamer)	Square wave voltammetry (SWV)	Mouse blood serum and urine	10–600 ng ml^{-1}	9.8 ng ml^{-1}	[23r]
Oxytetracycline	GCE modified with graphene oxide–polyaniline (GO–PANI) and horseradish peroxidase (HRP)/AuNPs/OTC-BSA/HRP-labeled aptamer	CV	Honey	4.0×10^{-6} mg L^{-1} to 1.0 mg L^{-1}	2.3×10^{-6} mg L^{-1}	[23s]
Penicillin	GCE modified with magnetic graphene nanocomposite (GR–Fe_3O_4NPs) and a poly (3,4-ethylenedioxythiophene)–gold nanoparticles composite (PEDOT–AuNPs) as the platform	DPV	Milk	0.1–200 ng mL^{-1}	0.057 ng mL^{-1}	[23t]
Penicillin	4-Nitrobenzenediazonium Salt modified screen-printed carbon electrodes (SPCEs)	EIS	Milk	0.4 and 1000 μg L^{-1}	4 μg L^{-1}	[23u]
Streptomycin	GCE modified with porous carbon nanosphere and multifunctionalgraphene composite (GR–Fe_3O_4–AuNPs)	DPV	Milk	0.05–200 ng/mL	0.028 ng/mL	[23u]
Streptomycin	GCE modified with porous carbon nanorods, gold nanoparticles and copper oxide functionalized multiwalled carbon nanotube composites	DPV	Milk and honey	0.05–300 ng mL^{-1}	0.036 ng mL^{-1}	[23v]
Streptomycin	Gold electrode with exonuclease I (Exo I), complimentary strand of aptamer (CS), Arch-shape aptamer	DPV	Milk and serum	30–1500 nM	11.4 nM milk and serum with LODs of 14.1 and 15.3 nM respectively	[23w]
Kanamycin	GCE modified with thionine functionalized Graphene and hierarchical nanoporous PtCu	DPV	Pork meat, Chicken liver	5×10^{-7}– 5×10^{-2} μg mL^{-1}	0.42 pg mL^{-1}	[23x]
Kanamycin	Gold electrode with self-assembled 5′-SH-modified kanamycin-specific aptamer was (folding induced aptamer)	SWV	Milk	10–2000 nM	0.014 nM	[23y]
Kanamycin	GCE modified with nanocomposite MWCNTs, the 1-butyl-3-methylimidazolium hexafluorophosphate (BMIMPF6) (ionic liquid), and amine-terminated Graphene (GR-CO-NH-CH2-CH2-NH2)	DPV	Milk	0.001–100 μM	0.87 nM	[23z]
Chloramphenicol	Gold electrode with self-assembled thiol-modified CAP-specific aptamer (folding induced aptamer)	SWV	Milk	1.6×10^{-9} to 4.2×10^{-7}	1.6×10^{-9} mol $L^{-1.}$	[24a]
Chloramphenicol	Gold electrode with aptamer hybridized with complementary biotinylated detection probe (aptamer/DNA duplex)	DPV	Real honey samples	1–1000 nM	0.29 nM	[24b]
Chloramphenicol	CAP-aptamer mixed with different types of gelatine was applied on the surface of disposable gold screen printed electrodes (SPE)	DPV	Milk	0.30–2.0 nmol L^{-1}	1.83×10^{-10} M	[24c]

cheese [25g]. Rohrbach and coworkers [25h] reported label-free impedimetric LYS aptasensor based on multi-walled carbon nanotube-modified screen-printed electrodes (MWCNT-SPEs) as substrate. LYS-aptamer modified with amine groups readily reacted with –COOH functional groups of carbon nanotubes and stabilized on the electrode surface. The impedimetric measurements proved an increase in average resistance RCT value after immobilization of aptamer on the modified electrode, because of repulsion between the aptamer baring negative charge and the anionic ferro/ferricyanide redox mediator. Later, the RCT relatively decreased upon

introducing LYS and its interaction with the aptamer leading to the access of redox mediator to the electrode surface and subsequent charge transfer.

In another report, Peng and coworkers [25i] developed impedimetric faradaic impedance spectroscopy (FIS) aptasensor based on target induced aptamer displacement by employing selective aptamer and its complementary sequence (DNA-Aptamer duplex) on a gold electrode. The aptamer hybridised after adding LYS, bonded to LYS and totally detached from the surface, which led to a considerable decrease in electron resistance in presence of redox mediator. The designed duplex scheme demonstrated better sensitivity with LOD of 0.07 nM compared to the previous scheme with 862 nM, despite providing more electroactive and conductive nanomaterial-based substrate. Similarly, Xia et al. designed aptasensor based on the target-binding-induced conformational change of aptamer-complementary DNA (cDNA) and investigated the impact of preparation method and density of the applied complementary DNA on the sensitivity of quantification by SWV. They suggested that single step preparation of the three-way junction structure generated by a ferrocene (Fc)-tagged cDNA bearing bulge abutted with 5 μM anti-LYS aptamer concentration provided better discrimination between currents attributed to signal on and signal off states, compared with step-wise procedures and 2 μM cDNA [25j].

Erdem et al. [25k] developed another impedimetric LYS aptasensor via modifying pyrolytic graphite edge (PGE) electrode with chitosan-graphene oxide (Cs-GO). The aptasensor was fabricated for integrating with disposable chip platform and results of the study yielded 28.53 nM LOD. Xiao and coworkers [25l] reported ultrasensitive impedimetric LYS aptasensor by preparing graphene (GR) substrate through coating GCE surface with CS/GO and applying hydrazine to reduce GO to GR. A high sensitivity and low detection limit of 6 fM was obtained owing to excellent electron conductivity of GR.

Gliadins and glutenin proteins found in wheat flour are the other important class of food allergens with immunoglobulin binding epitopes, which are responsible for some severe disorders, such as wheat-dependent exercise-induced anaphylaxis in adults and atopic eczema/dermatitis syndrome in children [25m]. In fact, allergy to wheat proteins encompasses a wide variety of disorders with different symptoms. According to exact classification, gluten-related disorders include 1) autoimmune disorders, such as celiac disease, gluten ataxia, etc., which may cause chronic diarrhea, weight loss or other symptoms, such as anemia, osteoporosis, neurological disturbances, 2) allergic, such as wheat allergy, usually affecting respiratory tract and skin, etc.; and 3) not autoimmune and not allergic disorders, such as gluten sensitivity [25n]. This has also reflected in lifestyle and diet preferences of non-sensitive individuals looking for healthier nutrition so that according to statics, ordinary people in USA not having disorders who preferred gluten-free food products have been constantly increasing, which have grown 3-fold from 2009 to 2014 [25o]. Recent few papers on electrochemical aptasensors may promise hope for intensive future efforts towards developing highly sensitive aptasensors and their commercialization.

Amaya-González et al. [25p] developed gli1-aptamer toward 33-mer gliadin protein and evaluated different modifications on the aptamer and their relation with dissociation constant through different techniques, such as the isothermal titration calorimetric (ITC), FIC, surface plasmon resonance (SPR), etc. The study demonstrated biotinylated gli1 aptamer as a better option for aptasensing compared to thiol-modified and 6-carboxy-fluorescein (6-FAM) as a fluorophore, because less Kd value alteration was observed upon this modification. Amaya-Gonzalez et al. [25q] developed competitive electrochemical aptasensing gliadin by immobilizing the 33-mer gliadin protein on magnetic beads and introducing gli4 aptamer in presence of solutions containing standard or sample gliadin and measuring the bounded aptamers by chronoamperometry after enzymatic labeling with strep-HRP, collecting beads via a magnet, placing on screen-printed carbon electrode and applying 3,3′,5,5′-tetramethylbenzidine (TMB). In a recent study, López-López et al. [25r] developed gluten aptasensor by immobilizing the biotinylated 33-mer protein on screen-printed carbon electrode (SPCE) through biotin-streptavidin binding. The detection scheme was based on competitive aptamer assay between aptamer binding to free gliadin in the solution and the 33-mer gliadin fixed on the electrode surface. Therefore, known amount of aptamer was introduced to the cell, followed by enzyme labeling, measuring the surface bound aptamer via quantification of the enzymatic product by chronoamperometry.

The other major and popular food allergen is peanut, which includes 13 potentially allergen proteins, Ara h1 to Ara h11, agglutinin and oleosin, Ara h1 and Ara h2 being predominant allergenic proteins [25s]. Tran et al. reported a selective aptamer for a major allergen, peanut allergen Ara h1, which was selected through capillary electrophoresis (CE)-SELEX and had 80 nucleotide-long with a dissociation constant in the nanomolar range [25t]. Trashin et al. [25u] reported impedimetric Ara h1 aptasensor by immobilising 80-mer thiol-modified selective aptamer on the gold electrode surface.

Milk is another possible source of allergens, especially for infants, which include toxic agents, such as caseins, α-lactoglobulin and β-lactalbumin. Several immunosensors have been reported toward milk allergens, with few reports of aptasensors and there has been no report on casein-binding aptamer so far (sensors-16-01863).

Eissa et al. developed aptamer selective toward β-lactoglobulin (β-LG) milk protein type A and B using SELEX method and evaluated binding affinity with fluorescence binding assays. Among evaluated aptamers, BLG14 aptamer sequence demonstrated higher affinity toward both types of β-LG, A and B with 82 and 80 nM dissociation constants, respectively. The aptamer was applied onto graphene screen printed electrode surface and integrated into electrochemical transduction system. The aptasensor was tested in spiked food extract via SWV in the presence of ferrocene redox mediator and detection limit of 20 pg/mL was achieved [25v].

Other classes of potential food allergens are lupin flour along with all the foodstuffs containing lupin as a food additive. The β-conglutin (Lup an 1) has been identified as major lupin allergen and was added to the list of mandatory food labelling products in 2008, due to several cases of allergy reports. Recently, efforts have been made to develop high-affinity aptamers for sensitive quantification of this allergen [25w,x]. Few numbers of detection assays have been developed exploiting aptamers, such as optical methods [25y] and Apta-PCR assay [25z], however, studies toward developing electrochemical aptasensing platforms for β-conglutin (Lup an 1) β-conglutin (Lup an 1) are still missing.

4.1.4. Detection of toxins

Ochratoxin A (OTA) the prominent mycotoxin is the most widely studied toxin by means of electrochemical aptasensors. It is present in a wide variety of food products and may pose several health threatening toxic effects, such as nephrotoxic, hepatotoxic, neurotoxic, teratogenic and immunotoxic activities [26a]. Mishra et al. developed a competitive aptasensing assay for determination of OTA in cocoa samples. The aptamer immobilised on the SPE through 4-carboxyphenyl diazonium activated with N-(3-dimethylaminopropyle)-N-ethyl-carbodiimide hydrochloride (EDC), and N-hydroxysuccinimide (NHS) and incubated with free OTA and biotin-labeled OTA to generate competitive binding

followed by introducing avidin-ALP as signal generating agent to form avidin-biotin binding. The dephosphorylation of 1-naphthyl phosphate (1-NP), a substrate for ALP, and its oxidation to 1-iminoquinone and related DPV curves was observed [26b]. A previously developed impedimetric aptasensor for determination of OTA in cocoa based on SPE with similar surface modification and with direct OTA aptasensing assay had exhibited rather lower sensitivity with LOD of 0.15 ng/mL compared to 0.06 ng/mL LOD for the competitive voltammetric aptasensor [26c]. Tong et al. reported the first OTA electrochemical aptasensor based on exonuclease-assisted target recycling amplification strategy, which was successfully applied on wheat starch samples and yielded low detection limit of 1.0 pg/mL [26d]. Aiming to determine OTA levels in corn samples, Tan et al. [26e] developed exonuclease-catalyzed target recycling aptamer assay based on repulsive electrostatic forces between negatively-charged ITO sensor surface and the methylene blue (MB)-tagged ssDNA-OTA aptamer duplex in the absence of OTA, and electron transfer after introducing OTA. The dissociation of aptamer occurred in presence of target and upon adding exonuclease, the degraded OTA aptamer and MB-tagged DNA, resulted in less negatively charged pieces, which initiated the electron transfer. Similar exonuclease assisted amplification strategy was employed in a recent study by designing a hairpin structure consisted of OTA-aptamer, extended DNA and the complementary sequence of the aptamer. The signal off state because of MB-tagged ssDNA in the proximity of ITO turned to signal on after incubating hairpin probe with OTA and applying the complex on the electrode surface followed by adding exonuclease [26f]. Other oligonucleotide-based amplification strategies, such as rolling chain amplification (RCA), have also been applied for sensitive detection of OTA in food samples [26g,h]. Several label-free impedimetric OTA aptasensor schemes have been designed in recent years. For instance, Evtugyn et al. [26i] immobilised thiol-modified OTA aptamers on Ag nanoparticles, which were decorated on the gold surface. The quantification was based on the conformational switch of the aptamer to G-quadruplex due to OTA-aptamer complex formation that led to the decrease in capacitance because of forming nonconductive structure and increase in charge transfer resistance because of surface compactness, which was measured in the presence of ferricyanide redox marker. The very similar sensor was developed by immobilising thiolated OTA aptamer on AuNPs suspended on the electrode surface and detection was performed based on increased resistance upon the binding event and conformational switch of the aptamer from linear to G-quadruplex structure [26j]. Rivas et al. [26k] developed OTA sensing substrate by incorporating IrO2 NPs as redox active agent and electropolymerized polythionine. In order to enable aptamer immobilisation, the electrostatic interactions between negatively charged citrate groups surrounding IrO2 nanoparticles and cationic amine-modified aptamer were used. The R_{ct} value increased after immobilising aptamer because of the repulsions between negatively charged phosphate backbone of aptamers and anionic redox indicator. Later, introducing OTA remarkably increased the R_{CT} due to anionic species formed by the ionisation of the phenolic and carboxylic groups in the OTA molecule, which added to the negative charge on the electrode surface (see Fig. 2).

OTA aptasensors based on competitive assays have been also developed aiming to achieve lower LOD by immobilizing aptamer on magnetic beads and incubating with HRP enzyme-linked OTA and free OTA [26l] and using both OTA-modified beads or aptamer-modified beads and incubating with free OTA and either OTA-ALP or aptamer-ALP depending on the designed scheme [26l].

Labelling aptamers with electroactive components other than traditional redox tags, such as MB have been rarely investigated. Loo et al. [26m] reported labelling OTA-aptamer with graphene oxide nanoplatelets (GONPs) via $\pi-\pi$ interactions between platelets and nitrogenous bases of the oligonucleotide. The strategy was based on the removal of aptamers after binding to the analyte and attachment of the dissociated GONPs from aptamers to the remaining aptamers and generating higher accumulation of electroactive component leading to enhanced current peaks. Subsequently, DPV reduction peaks of GONPs in the different concentrations of OTA were used as an analytical signal.

Several other classes of food contaminating toxins have been determined by SELEX-selected specific aptamers. The specific aptamer toward aflatoxin B1 (AFB1), the other key mycotoxin with carcinogenic effect, was selected for the first time in 2012 and integrated to varieties of optical and some electrochemical techniques [26n]. Aflatoxin M1 also classified as a carcinogenic toxin is produced by hydroxylation of aflatoxin B1 and is found in the milk of livestock consuming feed with aflatoxin B1 contamination [26o]. The selective and sensitive determination of this toxin, especially in milk and dairy products is highly critical. On the other hand, botulinum neurotoxins (BoNTs) also consist of highly dangerous life-threatening toxins produced by *Clostridium botulinum*, which can degrade intracellular proteins responsible for neurotransmitter vesicle docking leading to acetylcholine inhibition and consequently flaccid respiratory paralysis and death. These toxins can purposefully be added to food products as biologic weapons. Considering the hazards, efforts have been made for developing selective aptamers for determination of neurotoxins, such as BoNT type A [26p,q].

Endotoxin also called as lipopolysaccharide is a lipopolysaccharide–protein complex with amphiphilic and heat-stable properties and a key structural constituent of the outer membrane of the gram-negative bacteria, hence regarded as a marker indicating the gram-negative bacteria contamination [26r].

Table 2 has summarised recently developed electrochemical aptasensors for different types of toxins.

4.1.5. Detection of microbial pathogens

Diarrheagenic *E. coli* responsible for intestinal diseases are categorised to six different groups and the food-borne type is mainly associated with vero cytotoxin-producing *E. coli* (VTEC) and especially among the VTEC strains, *E. coli* O157: [H7] has been the most popular cause of food-borne outbreaks during last two decades [28a]. Shiga toxins initiate haemorrhagic colitis and the diarrhoea-associated form of HUS and are secreted by *E. coli* 0157: H7 and *E. coli* 0157: NM (non-motile) serotypes that are found in contaminated foods, especially those of bovine origin, including undercooked ground beef and unpasteurized milk [28b]. There have been several studies toward isolation of highly selective RNA aptamers for *E. coli* O157: H7 detection [28c,d]. The selection of high-affinity DNA aptamers for other strains of *E. coli* using whole-cell SELEX have also been reported [28e].

Zelada-Guille' et al. reported a potentiometric, ion-screening aptasensor based on amino-modified aptamer immobilised on carboxylated SWCNTs GCE for determination of nonpathogenic (*E. coli*) CECT 675 cells as a model for *E. coli* O157: H7. The potentiometric system consisted of working and reference electrode used to monitor the electromotive force (EMF) responses upon adding increasing concentrations of *E. coli* in standard samples as well as real samples, such as milk and apple juice spiked with the bacteria [18a]. Luo and coworkers explored target-induced aptamer displacement strategy and developed *E. coli O111* electrochemical aptasensor. After introducing target, the aptamer was detached from its complementary capture probe and later, streptavidin-alkaline phosphatase-tagged detection probe was added, which hybridised with the capture probe introducing analytical signals

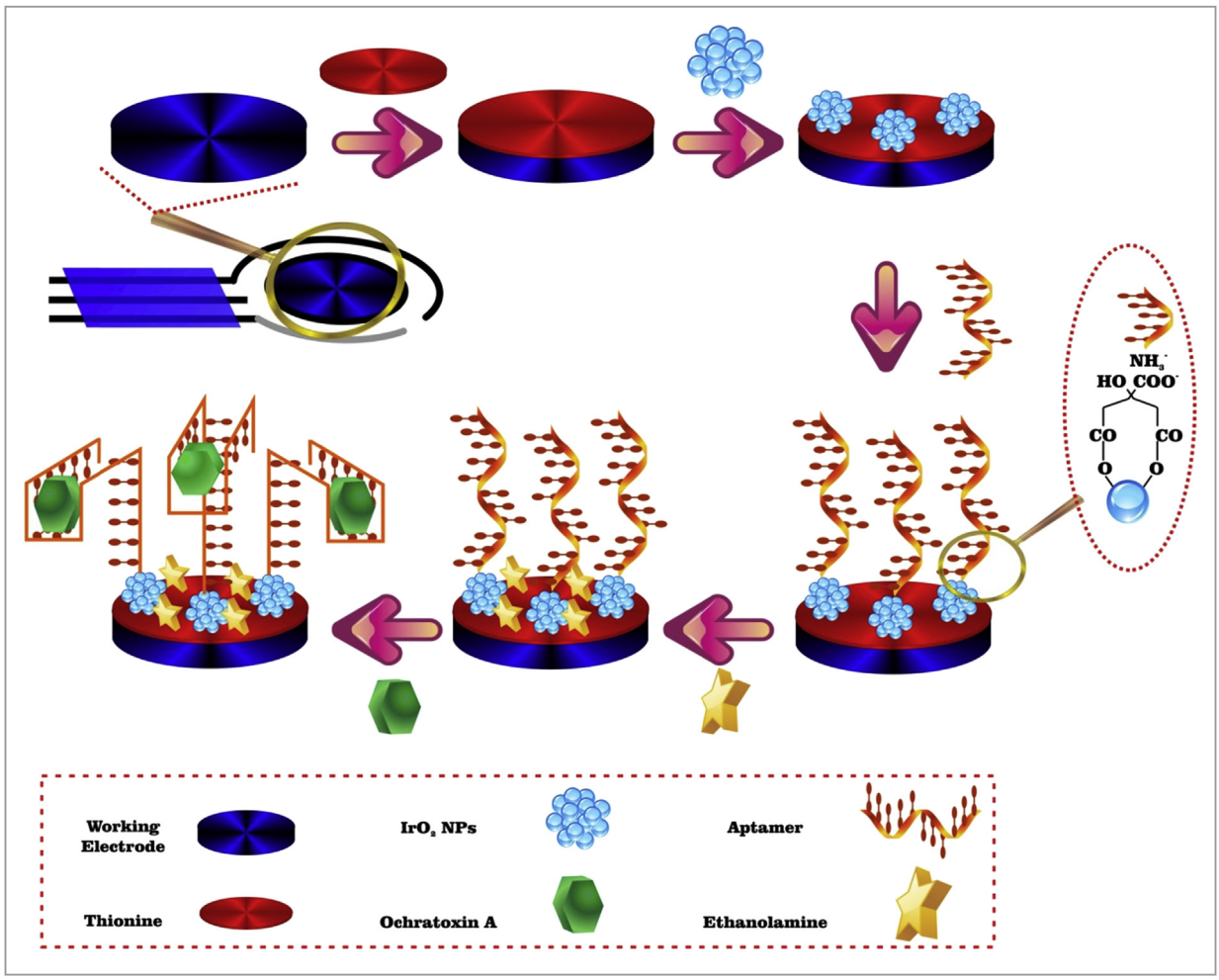

Fig. 2. Schematic view of the electrode preparation steps and sensing scheme based on impedimetric aptasensor for determination of ochratoxin-A (OTA). Re-drawing by Corel Draw 6.0 software.

Table 2
Recently developed electrochemical aptasensors against different food contaminating toxins.

Toxins	Electrode details	Electrochemical transduction	The real sample analysed	Linear range	LOD	Ref.
Aflatoxin B1	GCE modified with electropolymerized neutral red and polycarboxylated thiacalix[4] arene to covalently attach by carbodiimide binding	CV and EIS	Peanut, cashew nuts, white wine and soy sauce	0.1–100 nM for EIS	0.1 nM for CV and 0.05 nM for EIS methods, respectively	[26s]
Aflatoxin B1	TS-primer-AuNP-c-DNA was added to the stem-loop aptamer immobilised on gold electrode, underwent telomerase amplification and incubated with MB and aflatoxin. Second amplification was done by EXOIII-based catalytic degradation of ssDNA	SWV	Corn samples	0.0001–100 ppt	0.6×10^{-4} ppt	[26t]
Aflatoxin M1	Aptamer immobilised on Fe_3O_4/PANi-modified Pt-microelectrodes via glutaraldehyde	CV and SWV	Milk	6–60 ng L^{-1}	1.98 ng L^{-1}	[26u]
Aflatoxin M1	Amin-modified aptamer was immobilised on SPCE via diazonium bonding	EIS	Beer and wine	0.125–16 ng mL^{-1}	0.12 ng mL^{-1}	[26v]

(*continued on next page*)

Table 2 (*continued*)

Toxins	Electrode details	Electrochemical transduction	The real sample analysed	Linear range	LOD	Ref.
Aflatoxin B1	Gold electrode modified with Poly (amidoamine) dendrimers of fourth generation (PAMAM G4) and cystamine used to immobilize amino-modified aptamer	EIS	Peanuts-corn snacks	0.1–10 nM	0.40 ± 0.03 nM	[26w]
Aflatoxin B1	A hexaethyleneglycol-modified the aptamer was immobilised on an SPCE through carbodiimide immobilization	EIS	Milk	2–150 ng/L	1.15 ng/L	[26x]
Brevetoxin-2	Gold electrode modified with cysteamine and 1,4-phenylene diisocyanate. Was used to immobilise the target. The free target and fixed amount of aptamer were incubated with the electrode to establish competitive assay	EIS	Shellfish extracts	–	106 pg/mL	[26y]
Cylindrospermopsin	GCE modified with thionine-graphene (TH-G) nanocomposite and cross-linker glutaraldehyde (GA) used to stabilise amino-modified aptamer	EIS	Water from a local lake	0.39–78 ng/mL	0.117 ng/mL	[26z]
Endotoxin	Thiolated aptamer immobilized on gold disk electrode	EIS	–	0.01–1 ng/mL	–	[27a]
Endotoxin	Gold electrode modified with 3-mercaptopropionic acid (MPA) was used to immobilize amine-terminated aptamer	EIS	–	0.001–1 ng/ml	1 pg/ml	[27b]
Endotoxin	AuNPs electrodeposited on gold electrode and used to immobilize the thiolated aptamer	EIS	–	0.01–10.24 ng/ml)	0.005 ng/ml	[27c]
Endotoxin	AuNPs modified GCE used to immobilise hairpins and incubated with 1) the released DNA1 after adding target to the Au@Fe_3O_4, which was attached to aptamer and its complementary sequence, DNA1; 2) nicking endonuclease; 3) with Tb–Gra nanocomposite decorated with AuNPs	DPV	–	10 fg mL^{-1} to 50 ng mL^{-1}	8.7 fg mL^{-1}	[27d]
Endotoxin	AuNFs modified GCE immobilised HP2 () incubated with 1) the output DNA after reacting target with HP1 containing aptamer sequence 2)endonuclease 3) HP3/AuNPs/Cu-Metal organic frameworks (MOFs)	DPV	–	1.0 fg/mL to 100 ng/mL	0.33 fg/mL	[27e]
Fumonisins B1	GCE was modified with AuNPs and aptamer-DNA duplex was immobilised on the electrode. The graphene/thionine nanocomposites was attached to the aptamer as the signal tag	CV	Wheat samples	1–10^6 pg/mL	1 pg/mL	[27f]
Fumonisin B1	AuNPs electrodeposited on GCE used to stabilized thiolated aptamer	EIS	Maize samples	0.1 nM to 100 μM	2 pM	[27g]
Microcystin-LR (MC-LR)	Aptamer was immobilized on graphene-modified SPCE	SWV	Fish extracts and tap water samples	0.1 pM to 1.0 nM	1.9 pM	[27h]
Anatoxin-a	Disulphide modified aptamer was immobilised on Au electrode by self-assembly	EIS	Drinking water and certified samples	1–100 nM	0.5 nM	[27i]
Saxitoxin	Au electrode modified with Octadecanethiol/MWCNTs anchored with MB used to immobilise amino-linked aptamer	DPV	Mussel samples	0.9–30 nM	0.3 nM	[27j]
ToxinA (TOA) of Clostridium difficile	(HRP)-labeled aptamer with complementary DNA immobilized on Nafion–thionine–AuNPs-modified SPE	–	–	0–200 ng/mL	1 nM	[27k]

that were monitored by DPV. The performance of the aptasensor was tested in spiked milk and LOD of 305 CFU mL^{-1} was achieved, which was reported to be lower than 10^5 CFU mL^{-1} obtained by enzyme-linked immunosorbent assay (ELISA) [28f]. Another study for detection of *E. coli* was proposed based on developing selective aptamers toward proteins expressed on the outer membrane of *E. coli*. The impedimetric aptasensor demonstrated high sensitivity in the range of 1×10^{-7}–2×10^{-6} M and performed satisfactorily in water samples even in the presence of other contaminants [28g].

Salmonella spp. is another major food poisoning gram-negative bacteria especially found in poultry products. *Salmonella enteritidis* is the most widely affecting Salmonella with numerous cases of worldwide outbreaks, while *Salmonella typhi* and *Salmonella paratyphi* types are less widespread but have contributed to 50% of the Salmonella caused poisoning in developed Asian countries in the past decade [18b]. The excessive use of antibiotics has resulted in the emergence of multidrug-resistant Salmonella, which underlines the need for early stage detection through precise food control and its effective elimination [28h]. Several high-affinity aptamers have been selected for different classes of Salmonella, such as *Salmonella typhimurium* [28i,j], *Salmonella O8* [28k], *Salmonella enteritidis* [28l], *Salmonella paratyphi A* [28m], etc.

Labib et al. used cell-SELEX to isolate aptamers with high affinity toward live *S. typhimurium* by employing positive selection against live *S. typhimurium* and negative selection against heat-treated *S. typhimurium* and a combination of other related bacteria to impart the selected aptamer the discrimination capability between live and dead Salmonella. Then, the selected aptamer was integrated into the impedimetric system by immobilising aptamers on SPCE modified with gold nanoparticles. The aptasensor was capable of monitoring the live bacteria with a LOD of 600 CFU mL^{-1} [28n]. Mediator-free impedimetric *Salmonella* aptasensor was reported by Sheikhzadeh et al. based on immobilisation of amino-functionalized aptamer via carboxyl groups of poly[pyrrole-co-3-carboxyl-pyrrole] copolymer film coated on gold disk. The alterations in electrical features of the polymer upon target-aptamer binding were used as an analytical signal for detecting Salmonella [28o]. Jia et al. [28p] developed another Salmonella aptasensor by electrodepositing the composite of carbon nanotubes and RGO on GCE and immobilising the amino-terminated aptamer on the modified electrode surface. The impedimetric aptasensor demonstrated low detection limit of 25 CFU mL^{-1} (see Fig. 3).

In a recent report of impedimetric Salmonella aptasensor, diazonium modification of SPCE was applied followed by EDC (200 mM): NHS (50 mM) activation and stabilising amine-terminated aptamer on the electrode surface via carboxyl-amine bounding. The electrode was tested in spiked apple juice samples (1×10^2, 1×10^4 and 1×10^6 CFU mL^{-1}) and the LOD of 10 CFU mL^{-1} was obtained in standard bacteria samples [28q].

Another prevalent food-borne and the iatrogenic pathogen is *Staphylococcus aureus*, which is a gram-positive bacteria and responsible for varieties of diseases, such as septicemia, gastrointestinal tract infections and food poisoning toxic shock syndrome [28r]. Several aptamers have been isolated for determination of *S. aureus* as whole bacteria, using cell-SELEX procedure or aptamers sensitive toward epitopes expressed on the surface of *S. aureus* and its toxins [28s]. In an interesting study, Abbaspour et al. developed dual-aptamer-based sandwich assay against *S. aureus* by employing two aptamers, the first aptamer immobilised on magnetic beads and the second aptamer bearing AgNps as redox tag. After introducing the target and the generation of aptamer-*S. aureus*–aptamer-AgNps complex, AgNps were dissolved in acidic medium and measured by differential pulse stripping voltammetry technique [28t]. Jia et al. [28u] developed impedimetric aptasensor by modifying GCE surface with RGO and gold nanoparticles. The layer by layer assembly of rGO-ssDNA-AuNP was obtained followed by immobilising the aptamer on the surface of AunNPs (GCE/rGO-ssDNA-AuNP/aptamer). The ability of aptasensor for detecting *S. aureus* in real samples, fish extract and water, was demonstrated and the aptasensor could sensitively quantify bacteria in standard samples with LOD as low as 10 CFU mL^{-1}. Another graphene-based *S. aureus* aptasensor was developed using potentiometric transduction, which was capable of discriminating live bacteria. Two GCEs were employed, one was modified with graphene oxide (GO) and the other with RGO to compare the responses of each substrate based on EMF changes when aptamers immobilised on GO/RGO interact with different concentrations of *S. aureus*. The EMF-time plot depicted for two approaches showed better reproducibility despite high noise levels for GO, which stabilised aptamers through covalent binding compared to RGO, which immobilised aptamers via π–π interactions and offered lower detection limits. The reduction step for converting GO to RGO through hydrazine was defined as the reason for poor reproducibility of the RGO substrate [28v]. Recently, other potentiometric aptasensors with polycation-selective electrodes and protamine indicator have been reported for determination of bacterium, such as Listeria monocytogenes [28w], *Vibrio alginolyticus* [28x], etc.

4.1.6. Detection of other food contaminants (estradiol, melamine, bisphenol, etc.)

4.1.6.1. Phenolic contaminants. There are several evident on the correlation between animal and human bisphenol A (BPA) exposure and high risk of disorders originated from disruption in hormonal signalling roots, such as thyroid gland misfunctioning, insulin resistance leading to diabetes and immune dysfunction at the cellular level. Accordingly, the early exposure of the contaminants in infants by plastic toys and feeding utensils, during development is of high concern [29a]. The underlying reason for the endocrine disruption effects of BPA is its structure, which is analogue with endocrine hormones, estradiol and diethylstilbestrol, and capable of binding to oestrogen receptors [29b]. Recently, there have been increasing studies of BPA with electrochemical aptasensors. Deiminiat et al. developed multiwall carbon nanotubes/gold nanoparticles (f-MWCNTs/AuNPs) nanocomposite film as an electroactive layer on GE surface and as a substrate to immobilised thiolated BPA specific aptamer. The standard and real samples (such as mineral water, orange juice and milk) were studied by the proposed aptasensor with SWV technique and in the presence of ferrocene indicator [29c]. Some other direct electrochemical BPA aptasensing assays have been conducted by using electrode modification with the nanomaterial films, such as gold nanoparticles dotted graphene (GNPs/GR) nanocomposite film as a substrate on GCE [29d] and nanoporous gold film prepared with dealloying Ag from Au/Ag alloy leaves in concentrated nitric casted physically on GCE [29e]. In a recent study, Kazane et al. [29f] synthesised an anti-BPA aptamer modified with pentahistidine peptide in its 5′-terminal. The histidine tag was applied to immobilised the aptamer via noncovalent bonding on the polypyrrole modification of the electrode surface, which provided a close contact in molecular level with the electrode surface. The polypyrrole nitrilotriacetic modified GCE integrated into impedimetric transduction system and used to monitor BPA levels in the presence of $[Ru\ III\ (NH_3)_6]^{3+}$ complex conjugated with BPA aptamer.

Two common strategies of the conformational switch and complementary strand dissociation strategy were used in one aptameric assay with triple signalling feature for sensitive determination of BPA in the linear concentration range of 1–100 pM with a LOD of 0.19 pM. First, the thiolated ferrocene (Fc)-modified BPA aptamer was immobilised on GE and hybridized with the methylene blue (MB)-tagged complementary DNA probe (MB-P). Upon

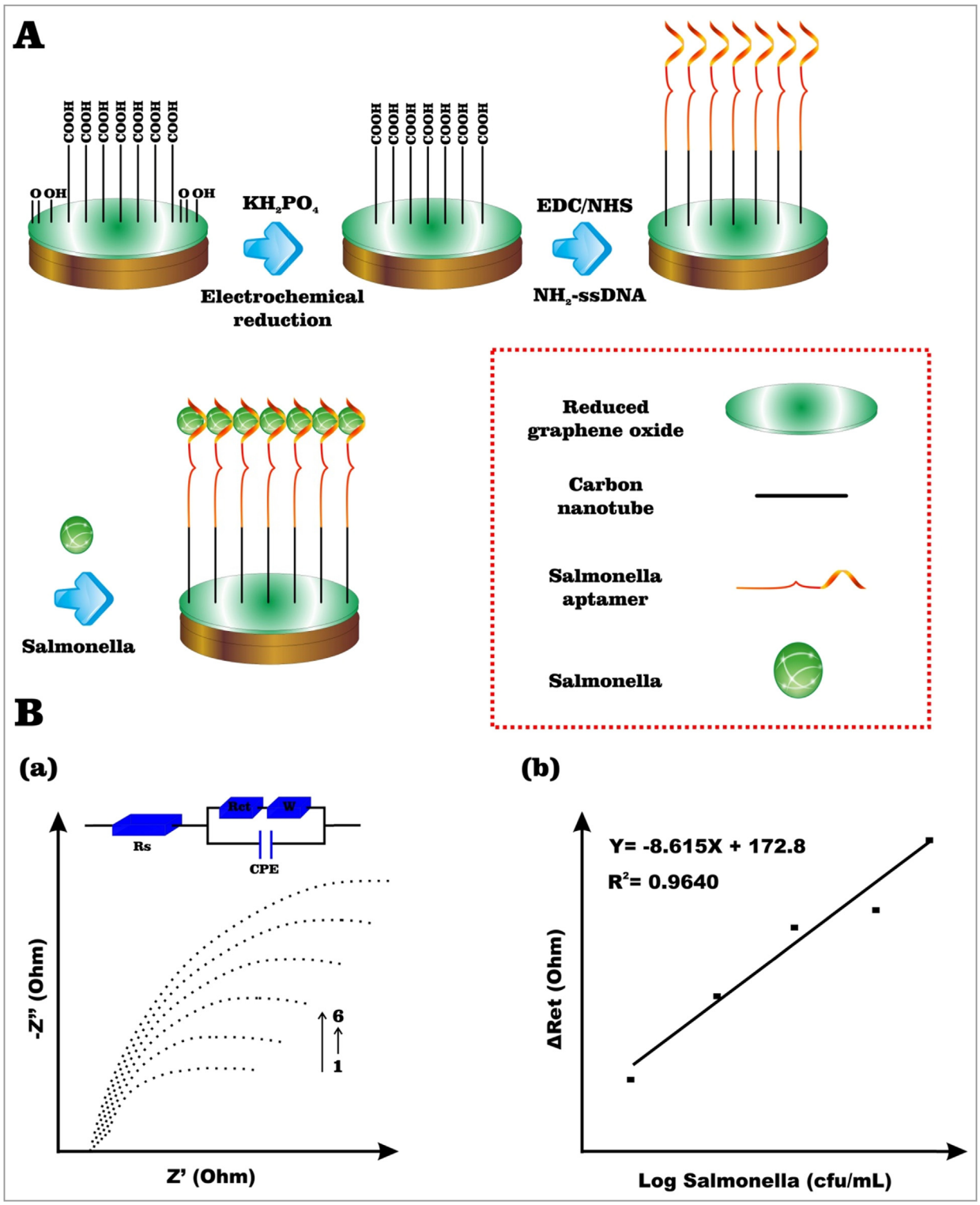

Fig. 3. (A) The schematic illustration of the modification of GCE surface and the Salmonella aptasensing assay. (B) Impedimetric results (a) Nyquist plots obtained for of the rGO-MWCNT-aptamer modified electrode with respond to different concentrations of Salmonella (from 1 to 7.5 × 10 5 CFU mL^{-1}) in 0.1 mol L^{-1} KCl solution containing 5 mmol L^{-1} $K_3[Fe(CN)_6]$ and $K_4[Fe(CN)_6]$ (pH 7.4); (b) The standard curve related to D-value resistance (ΔRet) versus different concentrations of the Salmonella. Re-drawing by Corel Draw 6.0 software.

introducing BPA, the MB-P was released, leading to decline in the MB signal and increase in FC signal because of the conformational switch of the aptamer after capturing BPA and getting closer to the electrode surface. Accordingly, the oxidation peak of BPA was observed as the third signalling pathway (see Fig. 4) [29g]. The label-free impedimetric BPA aptasensors based on a simple scheme of immobilising aptamer and complementary probe on GE was reported. The aptasensor was tested for its performance in spiked

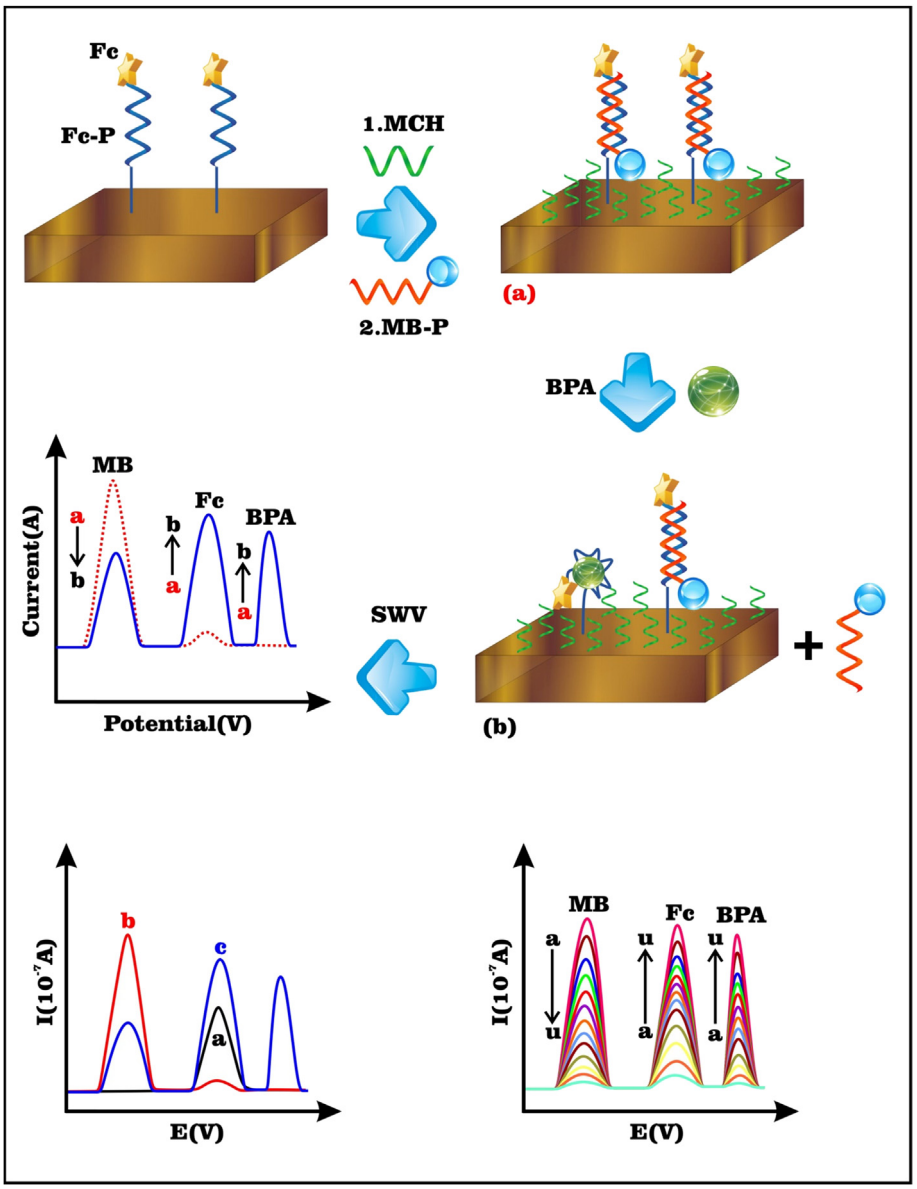

Fig. 4. (A) Schematic illustration for construction of the triple-signaling electrochemical aptamer assay toward BPA detection. (B) SWV curves comparing the signal response of different electrode modifications. (a) MCH/Fc-P/Au electrode, (b) MB-P/MCH/Fc-P/Au electrode, (c) MB-P/MCH/Fc-P/Au electrode incubated with 2 nM BPA. (C) SWV curves obtained for three electroactive components related to the detection of different concentrations of BPA. The concentrations are 0, 0.001, 0.01, 0.02, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.20, 0.30, 0.50, 0.80, 1, 2, 5, 10, 25 and 50 nM (from a to u).

drinking samples and LOD of 0.284 ppt was obtained in less than half an hour for standards hence, the aptasensor revealed a high potential for highly sensitive on-site detection of BPA in real samples [29h].

The other class of environmentally persistent food contaminants is PCBs, which have proven bioaccumulation and serious health risks, such as interference with the sexual hormone-mediated processes [29i], obesogen effect and metabolic impairment [29j] and intellectual disability in children exposed to PCBs [29k]. Pilehvar et al. reported electrochemical aptasensor for detection of hydroxylated PCB by modifying GCE with multi-walled carbon nanotubes (MWCNT) and immobilising selective amine-modified aptamer through amide binding. The characteristics of the aptasensor were evaluated with EIS, and a calibration curve was depicted after analysing standards with CV, which demonstrated LOD as low as 1×10^{-8} M [29].

Development of fast, sensitive and cost-effective electrochemical aptasensors for other widely encountered chemical contaminants, such as melamine, the popular milk adulterant, is expected in near future. In this regard, several recent reports on employing selective melamine aptamers with optical transduction systems are promising hope [29l–29n].

4.1.7. Hormonal contaminants

The increasing concerns about the hormonal contaminants in the environment and food products and their possible correlation with hormone-induced disorders, such as breast cancer, as some studies confirm, dictates avoidance of using these substances for increasing productivity of the meat supplied from farm animals. These hormones, which mainly include testosterone propionate, trenbolone acetate, estradiol, zeranol, progesterone, melengestrol acetate, and bovine somatotropin are allowed for livestock

treatment by FDA [30a], however, they have been banned for growth promoting applications since 1988 in the EU [30b]. 17β-Estradiol (E2) is the only hormone of the group, which have been widely studied by aptasensors based on mainly optical and some electrochemical methods. The few reports on estradiol detection were based on direct aptasensing without employing second complementary probe.

Fan et al. [30c] developed E2 aptasensor by incorporating the nickel hexacyanoferrate nanoparticles (NiHCF NPs) on GE as an alternative for redox indicator. The modification of the electrode followed by electrodepositing AuNPs and incubating with E2 specific aptamer to self-assembly. The voltammetric aptasensor performed satisfactorily in analysing spiked real samples and demonstrated high sensitivity with LOD of 0.8 pM in standard samples. In another study, the glucose oxidase modification on GCE was performed as redox indicator along with copper sulphide nanosheets and gold nanoparticles both for immobilisation of aptamer and second amplification through accelerating electron transfer. The DPV study on standards revealed high sensitivity and LOD of 60 fM [30d]. Ke et al. [30e] deposited micro gold dendritic structures on boron doped diamond electrode through dual template technique and employed for developing impedimetric label-free E2 aptasensor. Their proposed aptasensor offered very high sensitivity, the LOD of 5.0×10^{-15} mol/L and linear detection range of 1.0×10^{-14} to 1.0×10^{-9} mol/L. Another sensitive impedimetric E2 aptasensor in femtomolar range was constructed by Zhu et al. [30f], based on electropolymerization of poly(Py-co-PAA) film and applying EDC/NHS for activating carboxyl groups of the polymer on GCE.

5. Conclusion and future aspects

During recent decade, the promising features of the aptamers for varieties of applications either diagnostics and therapy have been revealed [31]. After some successfully commercialised electrochemical aptasensors for determination of food allergens, the hopes for employing this powerful analytical platform for determination of other health-affecting food contaminants are considerably raised. In this review, we attempted to attract the attention towards serious health hazards of the contaminants and highlight recent trends and novel studies for detecting these substances by electrochemical aptasensors. The combination of nanomaterials has been incorporated as the most preferred electrode modifications for providing high surface area for probe immobilisation and amplification of the signal response because of their excellent electrical conductivity. Toxins and antibiotics are by far the most widely analysed contaminants by several electrochemical aptasensors and detecting pathogenic bacterial contaminants and chemical phenolic substances are the next growing target areas.

Despite the vast number of recent reports, there are areas that require urgent attentions, for instance, gliadins with their expanded family are responsible for numerous types of allergies and unfortunately, the studies for developing efficient aptamers specific for this class of allergen is in its infancy. The same applies to other foodborne allergens namely, the milk allergen and lupin. The genetic manipulation of the food products is the other recent area of concern and should be addressed to prevent health consequences and fulfil the expectations of consumers, which are getting more aware of their rights for consuming healthier and organic food products. Meanwhile, the intensive studies should be focused toward developing highly efficient aptamers with sensitive electrochemical platforms for determination of any hormonal growth promoting agents along with chemicals that simulate the actions of hormones in the human body by competing for the same receptors. The other critical issue of food products is ethical aspects and its implication for different populations, such as Halal issue. The possible adulteration of the meat supplied from cattle origin with unauthorised species, such as porcine meat needs to be identified by analysing the relevant biomarkers (protein-based or DNA strand) through sensitive electrochemical aptasensors.

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