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Review Article

Aptasensors as promising new tools in bisphenol A detection - An invisible pollution in food and environment

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ABSTRACT

Owing to the endocrine disrupting effect, the detection of bisphenol A (BPA) is essential. Up to now, different chromatographic and spectroscopic analytical techniques have been developed for the detection of BPA, yet they are time-consuming, laborious and expensive. As a result, the development of a sensitive, specific and executive detection method seems vital. Recently, aptamers has been used as bioprobes of biosensors in a variety of targets. Much hopeful advancement in BPA aptasensors are being developed towards applications in food safety and environmental monitoring. In order to place these developments in outlook, this comprehensive review intends to present an overview on recent developed aptamer-based biosensors for the detection of BPA. Out of this review, trends in the development of colorimetric, fluorescence and electrochemical aptasensors for the monitoring of BPA are shown so that they will give a new idea for designing commercial kits. Finally, positive and negative points of each system are presented.

1. Introduction

Bisphenol A (BPA) is a synthetic chemical that is widely used as a monomer primarily in the production of epoxy resins and polycarbonate. Due to their property to resist high temperature (up to 145 °C) and their impact on strength and hardness, polycarbonates have different applications like water bottles, infant feeding bottles, toys, utensils, thermal paper and medical equipment [1,2]. Also, epoxy resins are widely used as protective coatings for food and beverage containers, paints, adhesives and electronic laminates because of their resistance to heat and chemicals [3]. The global production of BPA gradually increased from 5 to 8 million metric tons (MT) during the period 2010–2016 and is estimated to reach 10.2 MT by 2022 [4]. The routes of BPA exposure in human beings are mainly through ingestion, inhalation and dermal absorption. BPA migration from plastics to food is mainly seen when the canned food containers are heated for sterilization [3]. Inhalation of dust is also another source of BPA exposure. BPA impact on human beings includes cardiovascular problems, reproductive effects, mammary gland developmental problems, low sperm production, foetal growth restriction, anxiety and depression, obesity, hormone-related cancers like breast cancer or prostate cancer [5–7]. Being an endocrine disruptor, BPA can cause health impacts on humans even at very low concentrations [8]. BPA has a similar structure to that of oestradiol and diethylstilbestrol and thus can stimulate cellular response by binding with the oestrogen receptors. Also studies on laboratory animals showed adverse health effects even at low dosage of BPA [9].

This environmental pollutant may affect the development and reproduction of aquatic organisms in ecosystems. Also, it is responsible for the development of insulin resistance and has a potential role in etiology of metabolic disease, both for children and adults [10,11]. BPA has shown to bind to thyroid hormone receptors and perhaps has selective effects on their functions [12]. Most countries have forbidden BPA in baby dishes and other packing materials after 2010 [13]. According to the European Food Safety Authority (EFSA), Tolerable Daily Intake (TDI) amount for BPA is 4 μg kg^{-1} body weights per day [14].

Because of its serious adverse effect, it is so requisite to develop a reliable, remarkable selective and sensitive analytical method for BPA identification. Customary detection techniques for BPA like gas chromatography with mass spectrometry (GC-MS) and high pressure liquid chromatography (HPLC) exhibited some disadvantages such as intricate and time-consuming of sample pretreatments, expensive instruments and require trained operators [15–18]. So it would be highly suitable to develop rapid, simple, sensitive and field-portable alternatives for BPA

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detection to reduce the risk to public health. A typical sensor is composed of a transducer, with transforming the response into a detectable signal on modern systems. In addition, they have a chemically matching part that specifies the response of the target from its adjacent environment. Based on functional characteristics, they can be categorized as optical, electrical, mass or thermal sensors and they are used to sense desired analyte in the different matrices. A biosensor is a device that uses specific biochemical reactions mediated by isolated enzymes, immunosystems, tissues, organelles, whole cells or other biomolecules to detect different analytes usually by electrical, thermal or optical signals. The biological recognition part can have different entities like small organic molecules, antibodies or aptamers [19]. Recently, aptasensors have been presented as novel alternative assays to overcome constraints of conventional systems [20,21]. Aptamers are oligonucleotides sequences which have been provided by Systematic Evolution of Ligands by EXponential enrichment (SELEX) that can specifically bind to a variety of target molecules [22,23]. They have well-defined three-dimensional (3D) structures and have showed remarkable specificity and affinity [24]. In comparison with traditional chemical and immunological recognition agent like antibodies, peptides and enzymes, aptamers include various merits such as higher temperature stability, smaller size, simple labeling, easier artificial synthesis and modification [25–27]. Also, aptamers present the advantage of re-use over antibodies and peptide-based sensors for the attainment to multiple measurement of an exclusive analyte. So, because of these benefits aptamers have been with successfully used to detect various target analytes [1,28–30]. Additionally, they are considered as one of the most efficient biorecognition and therapeutic device [31]. The current state-of-the-art in the specific area of aptamer based sensing of BPA is presented. Employing nanomaterials in transducer as a part of aptasensor, they are able to boost signals resulting from target interaction with the aptamer. We also investigate advantages and disadvantages of different kinds of BPA aptasensors and in terms of quality in order to find out which designs can be the logical one. Comparisons between aptasensors via other sensors with different bio-recognition molecules such as antibodies, enzymes and whole cells showed in Table 1.

1.1. Aptamer-based BPA biosensors

Aptamers as promising new agents for both diagnostic and therapeutic applications include small single-stranded (ss) DNA or RNA ligands (with a molecular mass of 5–40 kDa). They offer valuable features including a wide range of targets, good reproducibility, low production cost and availability [37,38]. Aptasensor combined with a transducer and aptameras bio-recognition units can be used for quantitative measurement of an analyte [39–41]. The transducer changes the response of the recognition part into the relevant template of signal [42]. Moreover, chemical modification and labeling of DNA and RNA aptamers can be carried out to improve the detection system without affecting their affinity [43,44]. Moreover, designing aptamers by frequent cycles of denaturation and renaturation capability allow the retrieval of the function for reuse. Till now, various types of aptasensors have been introduced to detect and quantify BPA [36]. They are included optical sensors such as colorimetric [45], fluorescence [46,47], localized surface plasmon resonance (LSPR) [48], electrochemiluminescent [49] and electrochemical biosensors [50].

1.2. Optical aptasensors

Optical transductions have been employed in various biosensors. The applications is because of their ability to direct, label-free, and real-time detection of many chemical and biological substances [51,52]. An optical biosensor consists of a bio-recognition tool which has been integrated with an optical transducer system. Depending on the method of signal transduction, biosensors can be classified into different groups such as colorimetric, chemiluminescence, fluorescent and surface plasmon resonance. In the next part different types of optical aptasensors which have been developed for BPA will be discussed.

1.2.1. Fluorescence-based aptasensors

Fluorescence monitoring is attractive as it is a rapid, sensitive and specific technique. The emission of light by an excited molecules or nanomaterials during returning to their ground state is fluorescence. Nanomaterials have been widely used as probes indicators or labels/tracers in various bioassays due to their high sensitivity, wide response range and ease of operation [53]. Many fluorescent BPA sensing systems have been developed with aptamer as the recognition elements (Table 2).

1.2.1.1. Fluorescence based quantum dots aptasensor. Lee et al. developed a nano-aptamer assay being capable of detecting BPA, employing quantum dots (QDs), magnetic beads (MB), and a series of novel truncated aptamers [54]. The nano-aptamer sensor comprised of MB-QD565-aptamer complex was attached to signaling DNA-QD655. In

Table 1
Comparisons between aptasensors via other sensors with different bio-recognition molecules.

	Advantages	Shortcomings	Ref.
Aptasensors	Chemical synthesis of the aptamers is fast High sensitivity and low limit of detection Analyte affinity can be increased through more rounds of SELEX Can be developed for use in non-traditional solvents, temperatures, buffers	Determination of aptamer sequence via SELEX is very slow SELEX is very expensive Unmodified aptamersare vulnerable to nuclease degradation in serum	[31,32]
Immuonosensors	High sensitivity and low limit of detection High specificity and good selectivity Ease of preparation Elimination of costly devices Convenience in operation Widely used in clinical laboratory Robustness Economical for mass production	Minimal regenerability Detection need to solution to be compatible and non-denaturing Contain immunogenic regions Cannot be produced for any analyte Time-consuming Difficult to automate Poor precision	[33,34]
Cell based sensors	In comparison with molecule-based biosensors, the cell-based biosensor can provide additional information such as information associated with the pharmacology, cell physiology and toxicology of a sample Can be operate over a wide range of conditions such as various temperature and pH values Ease of miniaturization	Whole cell-based biosensors are not as sensitive to environmental changes as molecular-based ones Signal coming from the analyte of interest can be mask by sample components Emission from whole cell-based sensor can become unstable over time as the cells undergo leakage or diffusion Limited shelf life of live whole cells on a sensor platform Cryogenic conditions often reduce the viability as well as efficacy of sensing cells	[34]
Enzyme based sensors	Fast response time Good reproducibility Good stability High sensitivity and low limit of detection Ease of automation and miniaturization Minimal requirements for sample pretreatment High selectivity High purity of commercial availability The analyte of interest can be detected with different type of transduction systems such asthermal, optical and electrochemical	The active site of the enzyme is not readily accessible to the analyte Enzymes can be deactivated by some components in the sample The activity of enzyme is depends on temperature, ionic strength, Ph chemical inhibitors Some commercial enzymes are expensive	[35,36]

Table 2
Optical-based aptasensors for BPA detection.

Detection method	strategy	LOD	Linear range	sequence	Advent	disadvent	Ref
Fluorescence	Immobilization of probe DNA onto the optical fiber sensor surface	1.86 nM	2 nM to 100 nM				
5′-CCGGTGGGTGGT CAGGTGGGA TAGCGTTCCG CTAT GGCCCA GCGCATCACGGGC GCACCA-3′	A simple, very fast and one-step approach for BPA determination • on-site and real-time signal detection • cost-effective biosensor with effective surface regeneration	• Time-consuming of the immobilizing probe DNA onto the optical sensor fiber surface.	[45]				
Fluorescence	A label-free aptaseneore Based on molybdenum carbide nanotubes and anti-BPA aptamer	2 nM	2–20 nM	5′-CCGGTGGGTGGTCAG GTGGGATAGCGTTCC GCGTATGGCCCAGCGCA TCA CGGGTTCGCACCA-3′	• A label-free sensing approach for high sensitive and specific BPA detection in real water samples. • acceptable reproducibility • enzyme-free detection • low background signals of NMM dye due to use of Mo_2C nanotubes	• Time-consuming of the synthesis of Mo2C nanotubes	[63]
Fluorescence	Fluorescence resonance energy transfer (FRET) between fluorescein-labeled BPA aptamer and magnetic oxidation graphene (MGO)	0.31 nM	0.87–43.8 nM	5′- CCG GTG GGT GGT CAG GTG GGA TAG CGT TCC GCG TAT GGCCCA GCG CAT CAC GGG TTC GCA CCA-FAM-3′	• A simple and rapid method with good detection specificity • Low costly because MGO could be recycled for being reused • low-background interference, few fabrication steps and fast response • good performance of biosensore in 5 to 40 °C	• Time-consuming of the preparation of MGO sheets • Time-consuming of the fabrication of the MGO aptasensor • Small range of optimized pH	[47]
Fluorescence	Rely on Rolling Circle Amplification/Exonuclease III-Combined Cascade Amplification	5.4×10^{-17} M	1 nM - 0.1fM	5′-CC GGT GGG TGG TCA GGT GGG ATA GCG TTC CGC GTA TGG CCC AGC GCA TCA CGG GTT CGC ACC-3′	• Label-Free method • Using the amplification effect with an excellent signal • High sensitivity in trace concentration •Large signal to noise ratio	• High cost due to the consumption of enzim and addition DNA • Non Reusable biosensor • Need for much time to fabricate the operational • Aptasensor	[56]
Fluorescence	Modified NanoGene assay was selected as the sensing system where signaling DNA and QD655 was tethered to QD565 and magnetic bead via the aptamer	2.19 pM	2.19 pM to 4.38 nM	(24 bp, NH2-C6-T10-GGATAGCGGGTTCC)	• a palm-size nano-aptamer analyser system • on-system incubation, rinsing and fluorescence measurement • High sensitive assay with excellent selectivity • Low cost due to short sequence of aptamer	• Time-consuming of QD-aptamer preparation • - Time-consuming of the nanotracer preparation • Cost of construction, maintenance and repair of the analyzer for one target	[55]
Fluorescence	combination of toehold-mediated strand displacement and exonuclease III (Exo III) based signal protection strategy.	5 fM	10 fM to 10 nM	ND	• label-free sensing • cost-effectiveness • simple preparation • good practical applications in real sampls • no cross-reaction with BPA analogs • wide linear range	• Non-reuseable aptamer and biosensor • Complex construction strategy • Time-consuming of detection process and non-portability • low signal to noise ratio in real water • Need for much time to hybridize the aptamer with their complementary strands	[62]

(*continued on next page*)

Table 2 (*continued*)

Detection method	strategy	LOD	Linear range	sequence	Advent	disadvent	Ref
Fluorescence	IFE of AuNPs on the fluorescence of nitrogen-doped CDots	3.3 nM	10 to 250 nM and 250 to 900 nM	5′-CCG GTG GGT GGT CAG GTG GGATAG CGT TCC GCG TATGGC CCA GCG CAT CAC GGG TTC GCA CCA-3′	• relatively environmental-friendly because of the low-toxicity NCDots • performed at the high salt condition • have a good potential in environmental analysis. • using NCDots with superior optical properties, • The fluorescence intensity of NCDots did not change remarkably after 1 month. • do not need labeling or modifying aptamer	• Time-consuming of NCDots constraction	[59]
Fluorescence	fluorescence resonance energy transfer (FRET) between GO and FAM-ssDAN	0.219 nM	043–43.8 nM	5′- FAM-CCG GTG GGT GGT CAG GTG GGA TAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GCA CCA-3′	• Low cost strategy • low incubation time 15 min • no cross-reaction with BPA analogs • recovery range high • simple preparation • Ability to be portable • No need for use of the complex analytical instruments	• Time-consuming of GO preparation and its purification(about one week) • Non-reuseable aptamer and biosensor	[61]
Fluorescence	By means of aptamer, signaling DNA−QD655 was tethered to MB−QD565	0.731 pM	430–447.2 pM	$NH_2-C_6-(T)_{10}$-GGATAGCGGG TTCC	• Use modifled sequence and increase binding affinity • low cost due to short sequence of aptamer • High selectivity over BPA analogs • Satisfactory LOD	• Non-reuseable aptamer and biosensor • High incubation time for 16 h, and probability of detaching of the aptasensore • cost of using magnetic beads • norrow linear range • Time-consuming of QD-aptamer preparation	[60]
colorimetric	Cationic polymer aggregated AuNPs	1.50 nM	1.5–500 nM	5′-CCG GTG GGT GGT CAG GTG GGA TAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GCA CCA-3′	• A simple and label-free sensing approach • Using AuNPs with unique optical properties • No need for use of the complex analytical instruments and the time-consuming washing steps • Having great potential to detect other targets by using the appropriate aptamers	• nureuse of aptasensore • Small range of optimized pH	[46]
colorimetric	Aggregation/disaggregation property of AuNPs	0.43 nM	0.043–438 nM	5′–CCG GTG GGT GGT CAG GTG GGA TAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GCA CCA–3′	• one-step, label-free colorimetric aptasensor • Detection results can be visualized without the use of any instrumentation • reduced detection time and operation procedures • inexpensive, real-time monitoring and on- site detection of BPA	• Inability to reuse of aptasensore	[66]

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Table 2 (*continued*)

Detection method	strategy	LOD	Linear range	sequence	Advent	disadvent	Ref
colorimetric	surface Plasmon resonance shift of AuNPs underwent an electrolyte-induced aggregation in the presence of BPA.	0.004 nM	0.0043–4380 nM	5′-TTT TTT TTT TGG ATA GCG GGT TCC-3′,	• Rapid and labelfree detection of BPA detection of BPA • The aggregation of AuNPs-aptamer is observable by the naked eye • very low visual limit of detection • selective detection of BPA over a variety of BPA analogs • use in a screening procedure for food and environmental monitoring	• Non-covalent bonding between aptamer and AuNP • Need to salt electrolyte environment	[65]
Electrochemiluminescent (ECL)	Mn^{2+}-doped $NaYF_4$:Yb/Er upconversion nanoparticles was used in electrogeneratedchemiluminescence	0.16 nM	0.219–438 nM	5′-SH–CCG GTG GGT GGT CAG GTG GGATAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GCA CCA-3′ BPA-complementary DNA: 5′-biotin-CCC ACC TGA CCA CCC-3′	• a new platform for ECL applications based on the upconversion nanoparticles • highly selectivity and repeatability • no cross-reaction with BPA analogs with good recovery in comparison by HPLC method.	• Time-consuming of preparation of the complementary DNA-functionalized NaYF4:Yb,Er/Mn UCNPs • Time-consuming and complex fabricate of the aptasensor	[50]
ECL	Solid-state ECL sensing model rely on a target-responsive permeability gate	0.219 nM	0.219 to 2190 nM	ND	• a novel solid-state ECL sensing strategy based on a target-responsive permeability gate • high sensitive and label-free aptasensor with low background signal • the potential for a false signal often induced by quenchers can be eliminated due to the ‘‘signal-on’’ feature of the sensor.	• Time-consuming of the aptasensor preparation	[68]
ECL	signal-on ECL sensor combines the electrically heated electrode and the signal amplification of HCR	1.5 pM	2.0 pM-50 nM	5′CCG GTG GGT GGT CAG GTG GGA TAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GCA CCA3′	• label-free and signal-on ECL aptasensor • High sensitivity with wide linear range • in-situ detection capability	• High cost due to need to 4 different DNA Sequence for biosensor • Need to temperatures adjustment during the detection process • Time-consuming of the assembly of aptasensore • Need to 80 min to reaction time between BPA and aptamer	[73]
photoelectrochemical (PEC)	Immobilizing aptamer on the surface of Au/ZnO nanopencil photoanode	0.5 nmol L-1	1–1000 nmol L^{-1}	5′-(SH)-(CH2)6-CCG GTGGGTGGTCAG GTGGGATAGCGTTCCGC GTATGGCCCA GCGCATCA CGGGTTCGCACCA-3′	• a label-free PEC aptamer-based sensor • rapid and low cost technique for practical use in the detection of BPA in milk samples • A sensitive detection approach with excellent selectivity • appropriate in multiplex detection of trace level of contaminant in food safety	• Time-consuming and complex fabricate of the aptasensor	[49]

(*continued on next page*)

Table 2 (*continued*)

Detection method	strategy	LOD	Linear range	sequence	Advent	disadvent	Ref
PEC	aptamer immobilized TiO_2-Fe_2O_3 nanotubes	1.8×10^{-11} M	1.8×10^{-11}- 3.2×10^{-9} M	5′-GGG CCG TTC GAA CAC GAG CAT GCC GGT GGG TGG TCA GGT GGG ATA GCG TTC CGC GTA TGG CCC AGC GCA TCA CGG GTT CGC ACC AGG ACA GTA CTC AGG TCA TCC TAG-3′	• A simple and label-free sensing approach • Denaturation aptamer avoid using photoelectrode combined biocompatibility with visible light response • reusable and reproduceable biosensor.	• Time-consuming of preparation of nanotube • need to arc melting furnace under the protective atmosphere of argon gas to prepration of NTs	[74]
Surface-enhanced Raman scattering (SERS)	SERS-encoded aptasensor based on gold nanoparticle-nanorodheteroassemblies	16.77 pM	0.004 −4.38 nM	5′-SH-(T)10 CCGGTGGGTGGTCAGGT GGGATAGC GTTCCGCGTATGGCCCA GCGCATCACGGGTTCGC ACCA-3′	• A sensitive and easy approach with acceptable reproducibility • The low cost and fast technique with high potential • for on-site detection • No need for use of the complex analytical instruments		[70]
SERS	A selective aptasensor rely on SERS optical nanoprobes	3 nM	~3 − 300 nM	5′-CCG CCG TTG GTG TGG TGG GCC TAG GGC CGG CGG CGC ACA GCT GTT ATA GAC GTC TCC AGC-3′	• sensitive aptasensor with minimal perturbation of the aptamer's native, free-analyte binding. • having suitable efficiency for detection of trace levels of BPA in biological samples like blood with complex matrix	• impaired with high error in concentrations less than 3 nM for true quantitative analysis.	[69]
SERS	Employing double strand DNA- embedded Au/Ag core–shell nanoparticles	10 fM	100 nM to 10 fM	5′-Cy3CCG GTGGGT GGTCAGGTGGGAT AGCGTTCCGCGTATGGC CCAGCGCATCACGGGTT CGCACCA-3′	• ultrasensitive sensing approach for detection of BPA in tap water • highly sensitive limit of detection • wide concentration range • appropriate for field applications because measurement can be performed under aqueous colloidal conditions • Time-saving with no need for purifying steps	• Time-consuming and high constraction costs of aptasensore	[71]
surface plasmon resonance	surface plasmon resonance aptasensor based on AuNPs aggregation	4.3 pM	ND	5′-TTT TTT TTT TGG ATA GCG GGT TCC-3′	• Label free detection of BPA • rapid detection of BPA (30 s) • selective detection over a variety of BPA analogs • useable in screening procedure for food and environmental monitoring. • reliable performance for sub-ppb levels.	• ND	[75]
surface plasmon resonance	generate coupled localized surface plasmons (cLSPs) on optical fibres	330 ± 70 attoM	ND	ND	• ultra-low detection limit • direct detection of Bisphenol A • potential to be made portable	• ND	[76]
surface plasmon resonance	coupled localized surface plasmons from gold nano-antennae covalently modified with BPA aptamer	330 ± 70 aM	ND				
CCGGTGGGTGGTCA GGTGGGATAGCGTT CCGCGTATGGCCCA	• portable sensing platform • useable in remote sensing and potential multiplexing ability • direct detection of bisphenol	• Time-consuming of Fabrication of coupled localized surface plasmons sensors	[77]				

(*continued on next page*)

Table 2 (*continued*)

Detection method	strategy	LOD	Linear range	sequence	Advent	disadvent	Ref
GCGCATCACGGGTT CGCACCA	A						
LFA	• very good strategy to detection of small molecules at ultra-low concentrations • simple operating procedure dissociation of aptamers from the surface of AuNPs upon recognition of small targets and used the negatively charged BSA protein	50 nM	up to 1000 nM	ND	• A lable free, rapid, cost-effective and in situ means to BPA detection • effectiveness and efficient mechanism with simply fabricated • good selectivity against interfering molecules, and strong operation in river water samples. • applicable for the other targets detection through changing the corresponding aptamers	• Time-consuming of sample preparation • Data analysis with image processing	[72]

the absence of target, graft of the MB-QD565-aptamer with signaling DNA – QD655 is constant and no fluorescence emission was observed (Fig. 1). In the presence of BPA, strong affinity of aptamer to the target instead of the complementary sequence, leads to signaling DNA-QD655 release. Accordingly, the level of released DNA – QD655 and the corresponding decrease of QD655 fluorescence signal are directly proportional to the concentration of BPA. The new truncated aptamer showed better response with LOD = 0.17 pg/mL rather than the reference aptamer with LOD = 570 pg/ml [54]. However, it should be noted that the linear range in this method has been reduced (100 – 104 pg/mL). So, modifying the sequence and structure of the aptamer through removing nonessential nucleotides will greatly improve the performance of aptamer-based biosensors. The truncated aptamer has also presented the finest selectivity of BPA recognition over target analogues. Developed nano-aptamer assay with the modified aptamer can satisfy the analytical requirements related to BPA detection for environmental samples. The reasonable explanation can be that the sequence of the aptamers may impress the ability of the sensor by affecting the targeting ability of aptamer. However, the functionalization of magnetic nanoparticles (MNPs) can be complex and costly. Importantly, weak DNA hybridization and enzyme kinetics in the surface of MNPs are hindrances which may restrict their use in wide applications [55].

Carbon dots (CDots) as classes of carbon-based fluorescent nanomaterials have attractive properties such as solubility, photostability, and biocompatibility that are applied as ideal fluorescent probes [56,57]. Accordingly Wang et al. used nitrogen-doped CDots as fluorescence indicator for rapid detection of BPA in an inner filter effect (IFE)-based aptasensor [58]. In this strategy, the emission of fluoresce is significantly inhibited by dispersed gold nanoparticles (AuNPs) with IFE, while recovered when AuNPs aggregated. Targets-bound aptamer modulates the aggregation of AuNPs, and then controls the IFE efficiency for signal transfer. This method can reduce the analysis process by avoiding the separation and washing step to 35 min.

A substantial effort to develop a palm-size nano-aptamer analyser system for BPA detection was undertaken by Lim et al. by employed evanescent wave based system [59]. For this purpose, BPA specific aptamers (as DNA probe) were hybridized with the signaling of DNA-QD655. On the other side, magnetic beads (MB), encapsulated by the QD565, were conjugated with BPA specific aptamer. Upon incubation of BPA, the signaling DNA-QD655 conjugate was diffused from the aptamer and removed followed by rinsing. This way, the decreased fluorescence emission from QD655 is the feedback of the increased BPA concentration. In the concentration range of ppb BPA is detectable with this system [59].

1.2.1.2. Fluorescence based graphene oxide aptasensor. A novel aptasensor based on graphene oxide (GO) was validated for BPA screening in tap/river water samples with LOD of 0.05 ng mL^{-1}. The proposed system exhibited the linear range from 0.1 to 10 ng/Ml [60]. In this system GO selectively adsorbs and quenches the fluorescence produced by FAM-labelled ssDNA probe. By entering BPA, this molecule preferentially with high affinity binds with the aptamer and prevents the aptamer from adsorbing onto the GO surface. Important features of this system are optimization duration in 15 min, recovery range of 96.0% to 104.5% in spiked water samples, fine sensing efficiency at pH 7.0 to 8.0 and no cross-reaction with BPA analogs [60]. In particular, fluorescence resonance energy transfer (FRET) phenomenon occurred between a fluorescent donor and an acceptor. The magnetic graphene oxide (MGO) is formed by compounding magnetic Fe_3O_4 and an oxidized graphene (GO). Like GO, the MGO can suppress the fluorescence of fluorophore tags and adsorb single-stranded DNA selectively [46]. Accordingly, Yin Hu et al. developed BPA biosensor based on FRET between fluorescein-labeled anti-BPA aptamer and MGO. The presence of the BPA led to the combination of BPA aptamer with its target. Then, desorption of the aptamer from

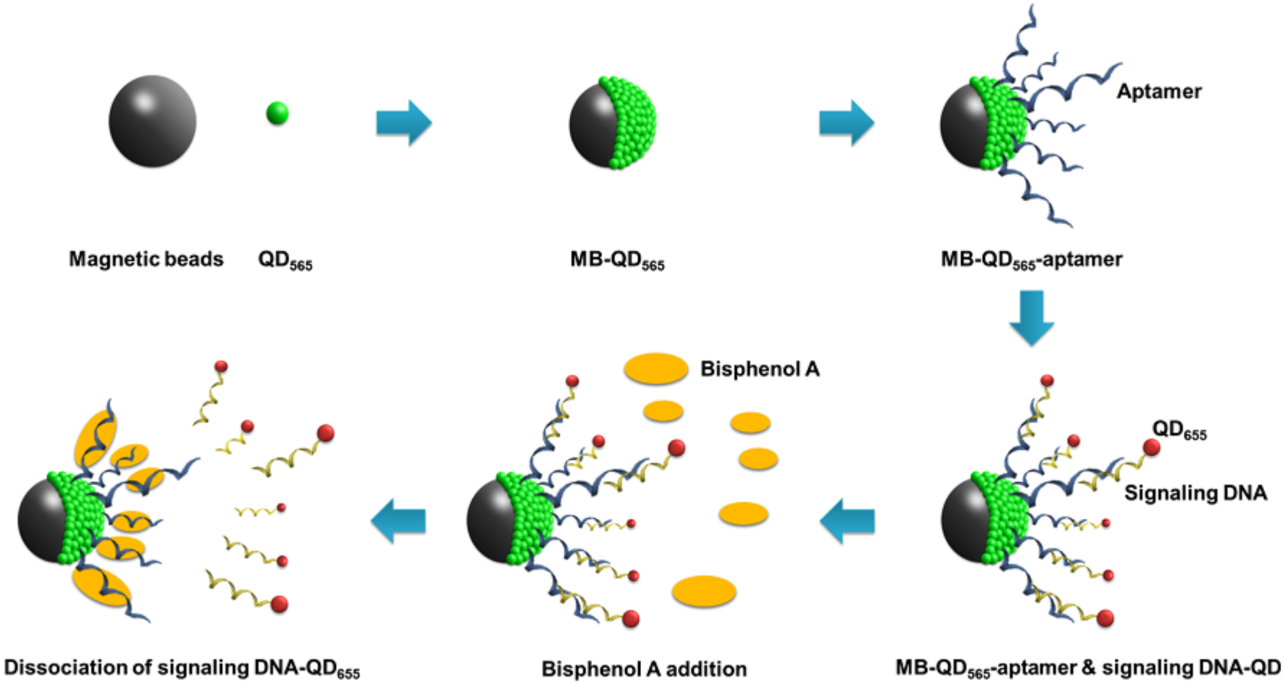

Fig. 1. Representation of the principle of the sensitive fluorescence aptasensor for bisphenol A detection. Reproduced from Ref [46]..

MGO results in fluorescence recovery. In this approach, the response time was 15 min [46].

1.2.1.3. Other fluorescence based aptasensor. In an interesting and different approach Chen and Zhou presented a label-free sensing platform based on Toehold-mediated DNA strand displacement (called a toehold) [61]. Toehold reaction is a non-enzymatic route in which one strand of double-DNA strand is exchanged with another strand. In this approach, DNA Y junction was used for the amplification system. As illustrated schematically in Fig. 2. In the absence of BPA, the stability in conformation of aptamer leads to impeded Toehold reaction and subsequently the Y-shaped junction formation. The low concentration of BPA leads to significant dsDNA Y-shaped molecular architectures. In order to fabricate the DNA Y junction, three hairpin probes were employed as the building blocks. So the cascaded signal amplification efficiency of toehold reactions and the signal protection capacity of Exo III, reproduce a considerably amplified fluorescence subsequent to being stained with SYBR Green I. Interestingly, LOD of the proposed aptasensor obtained was 5 fM. This system demonstrated a wide linear range and excellent selectivity. Also, the recovery and the relative standard derivations (RSD) ranged from 90 to 118% and 1.7 to 5.7%, respectively, revealing that the adverse interactions on the sensor analysis is negligible [61].

Hence, cascade amplification system can offer high amplified signal efficiency and a more elegant sensing technique that provides the capacity to accumulate thousands of ssDNA products. In a similar strategy, a label-free fluorescent aptasensor with cascade amplification was designed by Li et al. based on the rolling circle amplification (RCA)/Exo III [55]. As illustrated in Fig. 3, duplex DNA probes (RP), BPA aptamer and trigger sequence were designed for BPA identification and amplification of the signal. In the presence of target, trigger sequence was released from RP to induct RCA reaction as primitive amplification. Consequently, Exo III boosted auxiliary amplification with hairpin probes (GHP) that is provided when lots of “G-quadruplex” in lantern-like form. The zinc (II)-protoporphyrin IX (ZnPPIX) leads to increased fluorescence signals. The 5.4×10^{-17} M was measured as LOD for this amplified sensing system with high recognition ability and specificity of detection. 120 min was introduced as the optimum reaction time .In addition, the optimization of the GHP probe concentration was investigated and as a result, the 20 μM GHP probe was optimized in the following assay [55].

Nowadays, Mo_2C nanotubes with two-dimensional ultra-thin nanosheets have showed more active sites compared with other nanomaterials and were introduced as novel transition metal carbides. Also their well-constructed hierarchical hollow structure reduces the aggregation and area of overlap [62]. It has been confirmed that the Mo_2C nanotubes have high selective adsorbtion to ssDNA. In this case, He et al. reported a novel label-free platform, using Mo_2C nanotubes and an anti-BPA aptamer. In the absence of analyte, the anti-BPA aptamer was hybridized with a Help-DNA. Conjugation between the BPA aptamer and the Help-DNA led to the creation of a G-quadruplex between them. Subsequently, the G-quadruplex structure which is a guanine-rich sequence can attach to the small molecule dye N-methyl mesoporphyrin IX (NMM). The formation of G-quadruplex structure strongly enhanced the fluorescence of NMM. In the presence of BPA, the interaction between the aptamer and the target can alter the conformation of aptamerand prevent G-quadruplex forming, so the fluorescence quenches. Also, due to high adsorption of Help-DNA by the surface of Mo_2C nanotubes, the background signals have reduced [62].

In another fluorescence-labeled BPA aptamer, Yildirim and his coworkers developed an on-site, evanescent and wave-fiber-optic sensing system for BPA. In this system, the complementary probe of the target aptamer immobilized onto the surface of optical fiber sensor. The BPA containing samples was mixed with a certain concentration of fluorescence-labeled BPA aptamer. Then, the sample was exposed to the sensor surface, and a higher concentration of BPA created lower fluorescence signal. Under the optimal conditions, the sensitive response to BPA in this system was in the range of 2 nM to 100 nM. For all subsequent analyses, six minutes was optimized as incubation time. It was showed that the proposed system can be re-used for more than one hundred times [36].

1.2.2. Colorimetry-based aptasensors

Colorimetry sensing has been widely accepted as a selective and sensitive detection method for various analytes. A colorimetric sensing is used for rapid and naked eye detection of an analyte [63,64]. Current

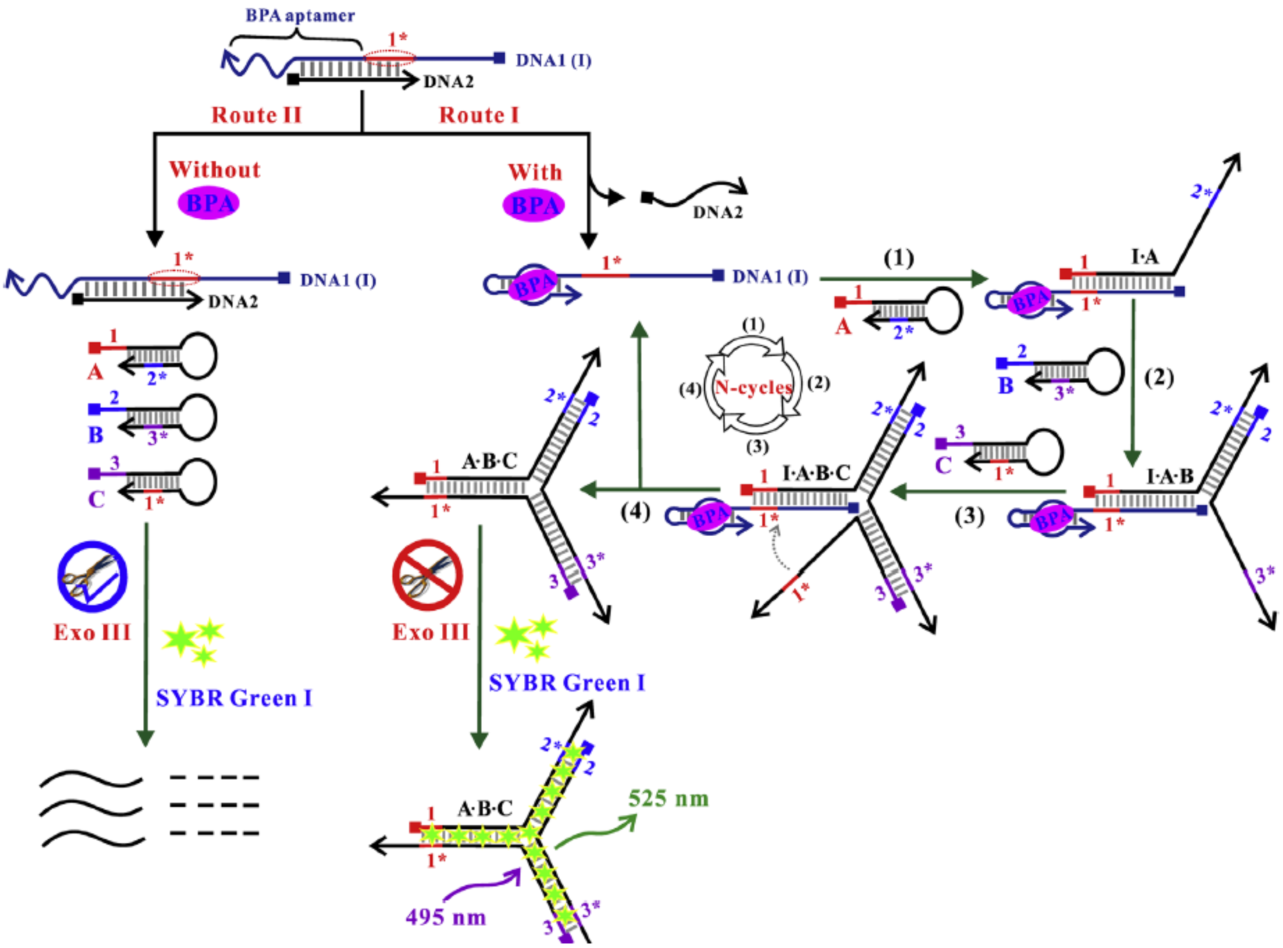

Fig. 2. Schematic of the designed strategy for amplified detection of BPA on the basis Toehold reaction and ExoIII. Reproduced from Ref [52].

colorimetric technology has developed the miniaturization of size and cost without any additional instruments [63]. Nanotechnology performs the main role in high-tech sensors. Namely, metal nanoparticles like gold (Au) have been extensively used in visual detection, owing to its unique optical property. By using the aggregation/dispersion property of AuNPs, the presence of an intended analyte can be monitored. The effect of salt has been showed on aggregation/disaggregation state of AuNPs. Optically, during the aggregation, the color of the AuNPs solution alters from pink to purple and the characteristic of Plasmon peak of AuNPs changes accordingly. Employing this merit, the one-step, label-free colorimetric aptasensor was effectively used to determine the quantity of BPA in real water samples by Mei et al. [65]. BPA aptamer was appended to AuNPs to protect AuNPs and maintains good tolerance of AuNPs in high salt concentrations. Upon the incubation of BPA in the protected-AuNPs system, the AuNPs would aggregate by competitive binding of aptamer and BPA resulting in a decrease in salt tolerance detection results can be observed by means of aggregation-induced color change in high salt concentration without utilizing any instrumentation. The LOD of system determined 0.1 ng/mL by naked-eye [65].

In a similar approach, Zhang et al. designed a very classical aptasensor with LOD of 1.50 nM based on label free anti-BPA aptamer and cationic polymer that induced aggregation of AuNPs [45]. Briefly, the concentration of cationic polymerpoly (diallyl dimethyl ammonium chloride) (PDDA) induced AuNPs aggregation. Specific BPA aptamer can hybridize with PDDA cationic polymer and lead to a duplex structure due to electrostatic attraction. Upon adding AuNPs, red wine would remain, due to the exhaustion of PDDA. After the formation of the BPA-aptamer complex, redundant aptamer reacted with PDDA, and ultimately remained PDDA could induce the AuNPs aggregation. Their proposed strategy indicated linear response ranging from 1.50 nM to 500 nM. When BPA concentration is more than 150 nM, this assay is able to detect analyte with naked eyes [45].

1.2.3. *Chemiluminescence-based aptasensors*

In the electrochemiluminescence (ECL) assays, electrochemically generated moderators undergo a high exergonic reaction to create an excited electron that caused light to emit from luminophores. These electron-transfer reactions allow the excited states of luminophores to be created without photo excitation. This system has provided a powerful analytical technique for food monitoring, environmental monitoring, clinical diagnostics and biomolecules owing to its benefits of suitable stability, rapid response, low price, high sensitivity, and low background [66]. As ECL luminophores, AuNPs, QDs, carbon dots and upconversion nanoparticles (UCNPs) have showed ECL effect. In one study, the labeled aptamers with the developed ECL nanomaterials $NaYF_4$:Yb,Er/Mn UCNPs were used for the detection of BPA [49]. This system was developed by assembling the complementary DNA-functionalized $NaYF_4$:Yb,Er/Mn UCNPs, BPA aptamer, and AuNPs-modified electrode through hydrogen bonds that represented an intense and stable ECL emission [49]. Employing ECL, Chen et al. developed a novel method based on a target-responsive permeability gate to determine BPA using polyelectrolyte–aptamer film deposited on the solid-state ECL electrode [67]. In this ECL sensor, The Au–g-C_3N_4, as ECL nanoemitter, was used to modify the electrode surface. Then polyelectrolytes thin films containing aptamers were assembled on the top of ECL film. When aptamers incorporated into the polyelectrolyte layers, they could maintain their affinity for the cognate targets. Conformational switch of

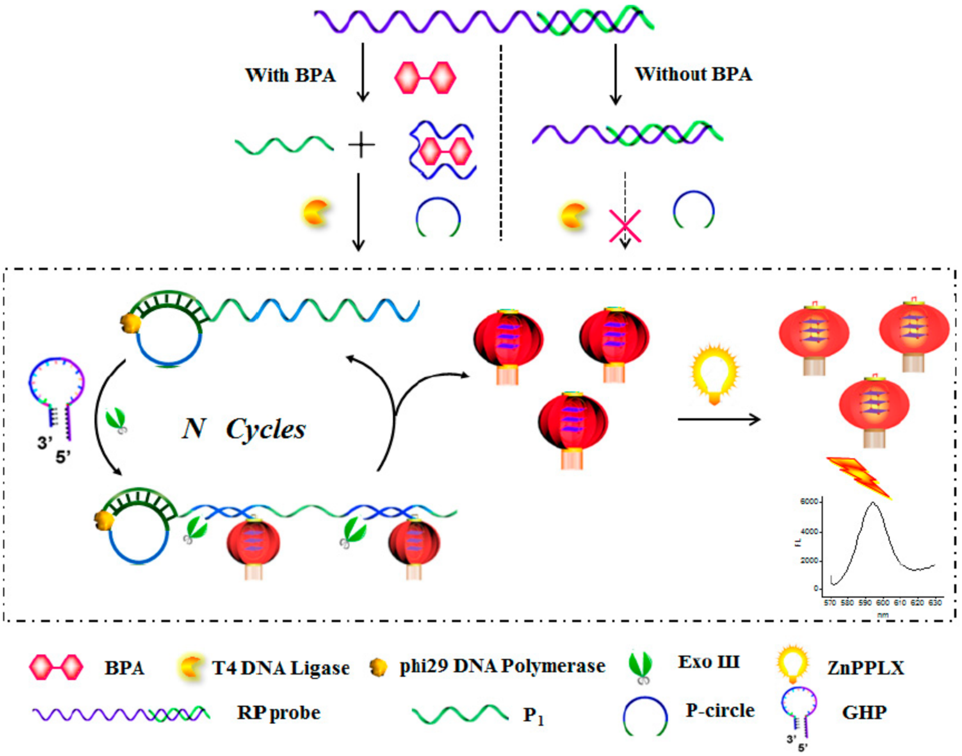

Fig. 3. Schematic outline of the principle of the fluorescent aptasensor for bisphenol A (BPA) based on the rolling circle amplification (RCA)/Exo III-combined cascade signal amplification strategy. Reproduced from Ref. [47].

the aptamer after binding to its target could increase the permeability of the polyelectrolyte film which is needed to trigger ECL [67].

1.2.4. Photoelectrochemical

The develope of photoelectrochemical (PEC) analysis has led to a significant advancement in bioanalytical efficiency and bio-detection methods. In PEC detection systems, a photoactive working electrode creates photocurrent signal under photo irradiation. Different semiconductors such as TiO_2, CdTe, CdS, ZnO and CdSe have high photocatalytic activity. These compounds have been used to produce photoelectric signals [48].

Accordingly, a label-free PEC aptamer-based sensor was fabricated by fixing BPA aptamer on the surface of the nano-Au/ZnO photoanode. In the presence of BPA and changes in the conformation of aptamer, the obstruction of photogenerated electron-transfer channels occur. In this mechanism and under the optimized conditions, the developed aptamer-based PEC sensor had a detection limit of 0.5 nmol L^{-1} and a linear range of 1–1000 nmol L^{-1}. Moreover, this PEC aptasensorhad been applied in liquid milk and tap water samples and displayed great performance in food analysis [48].

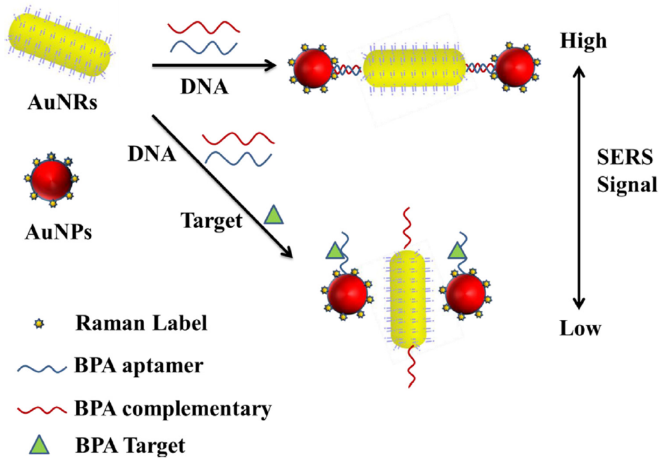

Fig. 4. Scheme of SERS aptasensor for the detection of BPA based on gold nanoparticle-nanorod hetero assembly. Reproduced from Ref. [60].

1.2.5. Surface-enhanced Raman scattering

Surface-enhanced Raman scattering (SERS) is a biosensing approach that enhances the intensity of the vibration spectra of an analyte by electromagnetic enhancements when it is close to a plasmonic surface like metallic colloidal nanoparticles. A SERS nanoprobe needs three conjugated part: (1) a protective part for stabilization of particle, (2) a Raman label molecule for quantitative recognition, and (3) a biorecognition element for specific assay [68].

SERS has intrinsic advantages, including high sensitive sensing capability over a broad range of excitation wavelength, reduced photobleaching, and narrow bands. So, SERS technique based on controllable separate nanoparticle assemblies needs to increase the Raman signal reproducibility and the intensity. Therefore, gold nanoparticle-nanorod was established by the assembly of AuNPs to the ends of AuNRs by Feng et al. [69]. As illustrated in Fig. 4, the BPA aptamer was attached to the ends of the AuNRs. Then its complementary DNA was conjugated on AuNPs surface which has been modified with SERS label molecule. After the hybridization of DNA, the AuNRs-aptamers were joined with AuNPs complementary. In the presence of the target, strong affinity of aptamer to target results in the assemblies dissolved gradually. Therefore, with the increase in BPA concentration, SERS intensity was decreased significantly. The high electromagnetic increment in narrow gaps between metal nanoparticles led to obvious Raman signals [69].

Another conceptually aptamer embedded SERS NPs was fabricated by Chung et al. for the detection of BPA in water. In this strategy, SERS-based detection system employed dsDNA (include cys3-BPA aptamer and thiolated probe DNA) embedded Au/Ag core–shell NPs. Like the previous work, with an increase in BPA levels SERS signal intensity

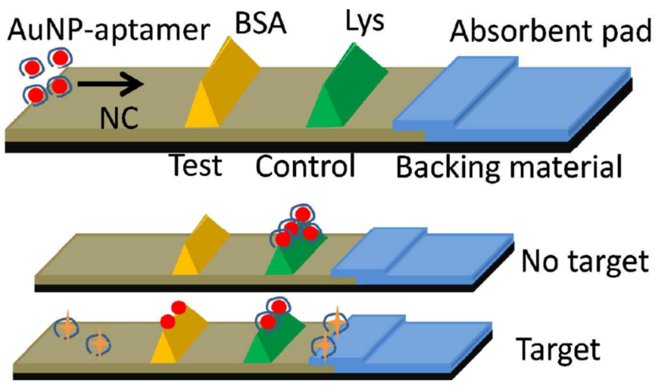

Fig. 5. Schematic representation of bisphenol A detection principles in aptamer based lateral flow test strip method. Reproduced from Ref. [62].

gradually decreases due to the Raman reporters of Cy3-labeled aptamer molecules [70].

Also, in order to quantify BPA in beverage, food plastic packaging and in the blood following human exposure to the toxin, a SERS-active nanoprobe with specific affinity to a BPA aptamer was characterized by Marks et al. which could be increased raman signal intensity through nanoparticle aggregation. This SERS system can detect as low as 600 fM [68].

1.2.6. Lateral flow assay

LFA methods can offer a fast and cost-effective qualitative means for the analysis of a target in situ. In this method wicks transport of sample by capillary along porous substrates in which immobilized specific recognition elements, e.g. antibody probes leads to accumulate to appearance a visible stripe in the presence of target. Since small target molecules like toxins have less complex structure than proteins, they are normally unable to form a complex with more than one antibody and create a strong sign. Also, considering their incongruity for small molecule, antibodies have some disadvantages as recognition agents including instability in no buffered solution, no physiological environments and high production cost. Recently aptamers have been used as recognition agents in sandwich-type LFAs [71].

For small molecules like BPA, Alsager et al. reported a simple LFA design where specific adsorption of aptamer to its target induced nonspecific adsorption of AuNPs as obvious lines on a nitrocellulose strip [71]. Recognizing BPA induced to the separation of aptamer from the surface of the AuNPs and absorbed on a test line by the bovine serum albumin (BSA). In the absence of BPA, aptamer coupled the AuNP pass with the test line due to the negative charged of aptamers and negatively charge of BSA in test line. Instead aptamer coupled AuNP trapped at a control line containing the lysozyme that is positively charged during the measurement process and captures all the AuNPs not considering the aptamers presence (Fig. 5) [71].

We summarized the progress that has been made in aptamer-based optical detection of BPA. These aptasensors have been listed in Tables 2.

1.3. Electrochemical-based aptasensors

In electrochemical detection systems, a redox reaction that occurs on electrode surface produces changes in electric current. Electrochemical aptasensor consists of an aptamer as a biorecognition element with the electrochemical transducer [77]. In comparison with optical aptasensors, electrochemical aptasensors offer merits such as requiring low sample quantity, simplicity, cost-effectiveness and reproducibility [78]. In the next section, we discussed new trends in BPA electrochemical aptasensors development.

1.3.1. Electrochemical aptasensor based on gold electrode

In 2012, Xue and his co-workers developed an electrochemical aptasensor to sense the trace level of BPA in water samples. Here, BPA aptamer and its complementary DNA are attached on the gold electrode via self-assembly and hybridization, respectively. Methylene blue embedded on the dsDNA as the redox tags. The detection of BPA was carried out by the competitive recognition of BPA while using immobilized aptamer on the surface of the electrode and the release of cDNA from the electrode. So the decrease of the redox peak currents was an indicator in quantitative detection. The LOD of the proposed system was 0.284 pg mL^{-1}. In addition, recovery values were obtained from 93.7% to 102.9% in spiked samples [79].

As sensing element, CNTs exhibited valuable features. Because of the remarkable sensitivity of their band gap energies to the redox environment or local dielectric, semiconducting single walled CNTs are sensitive to their chemicals [80,81]. One of the hindrances in the field effect transistor (FET) sensors which relied on CNT was detectingnonpolar small molecules.

Accordingly, in a novel strategy on aptamer sandwich-based carbon nanotube, a portable aptasensor for general molecular detection was created by Lee et al. [82]. The conductance change of swCNT-FETs can be explained by Schottky barrier modulation. Any charged analytes that are adsorbed onto the Au electrode can cause a change in the Schottky barrier height between the swCNTs and the electrodes, resulting in electrical sensor responses. The surface of Au electrodes in the swCNT-FET devices were functionalized with an anti-BPA aptamer to produce a sensing system relied on swCNTs. When the BPA molecules were adsorbed onto the aptamer residing on the Au electrode of the swCNT device, the charge in the labeling aptamer bound to BPA changed the work function of the Au electrodes. Such a work function change induced an increase in the Schottky barrier between the swCNTs and the Au electrodes, resulting in a reduction of source–drain current. In order to add more charges to the pre-treated aptamer, the anti-BPA aptamer modified with biotin at its 5′-end that enhance the detection limit of the sensors down to 10 fM. The strategy of overcoming fundamental limitation of FET-based sensors using carbon nanotube transistors as well as detecting non-polar molecular species. It should be mentioned that this system is attributed to two important features. First, the negative charges of aptamers increased the signal to the SWCNT-FET device. Second, the sandwiched aptamer technique significantly enhanced the selectivity of the sensor with the requirement to binding of two aptamer simultaneously [82].

Previous electrochemical aptasensor studies reported that a dual-signaling system is an important strategy to produce response signals. Targets with redox ability are able to provide an extra signal. Based on this interesting triple-signaling strategy, Yu et al. illustrated a new type of BPA sensor employing dual-signaling strategy and the direct detection of the redox target (Fig. 6) [83]. A ferrocene (Fc)-labeled BPA-binding aptamer probe (Fc-P) was attached to the electrode surface and then hybridized with the MB-labeled complementary probe (MB-P). After target was added, MB-P was released from electrode surface, because of the conformational change of Fc-P. The proposed system exhibited linear range from 1 pM to 100 pM and a detection limit of 0.19 pM. The bioactivity of electrodes conserved after two weeks of storage at 4 °C [83].

Several integrated microfluidics analytical methods for detection of targets have been reported that are expected to enhance analytical efficiency by reducing the time, consumption of samples as well as portability and automation. BPA aptasensor based on integrated microfluidics with the electrochemical sensing method was represented by Kashefi et al. [84]. Briefly, the ferrocene labeled aptamer is immobilized on a nanostructured gold electrode with S-H bond. Then, a microfluidic channel is installed over the electrode. BPA was introduced and enriches the aptasensor by the GASI chip that creates micro-vortex in the microfluidic channel. Upon aptamer configuration change, Fc tag closes in to the electrode surface and oxidation signal of Fc and BPA

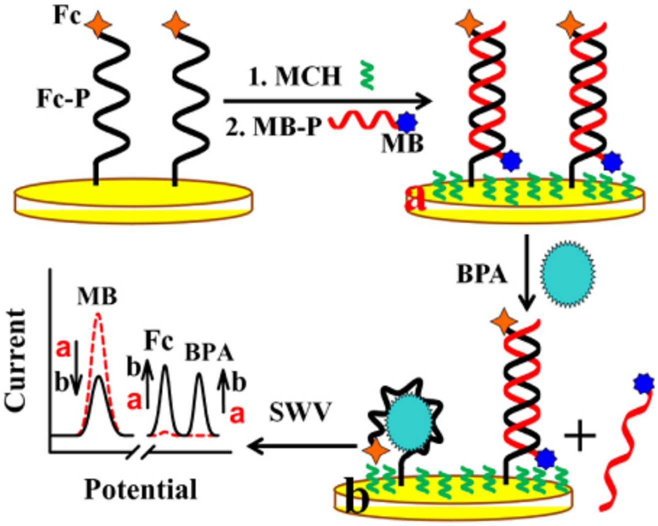

Fig. 6. Schematic illustration of the triple-signaling E-AB sensor for BPA assay. Reproduced from Ref. [72].

werecreated [84].

Terminal deoxynucleotidyl transferase (TdT) is a DNA polymerase that makes a long ssDNA through repetitive catalyzes of deoxynucleotide triphosphates at the 3′ terminal of DNA. The aptamer target complex inhibits the access of TdT to aptamer's 3′-end. Using this strategy, Abnous et al. introduced an aptasensor that could detect the target by detecting the limit of 15 pM [85]. In the absence of BPA, the poly T generation at the 3′-end of the aptamer hybridized with poly A of the complementary strand causes the formation of the bridge on the electrode surface that leads to low access of $[Fe(CN)_6]^{-3}$ as redox agent to the electrode surface [85].

Self-supported nanoporous gold (np-Au) microelectrode with 3D continuous nanoporous structures possess a tremendously large specific area, clean surface, high stability and biocompatibility, bringing about significant benefits in both molecular recognition and signal response [86,87]. To use these advantages in BPA detection, Shi et al. constructed electrochemical aptasensors with Exo III induced signal amplification [88]. As shown in Fig. 7, trace amount of BPA induce the separation of messenger DNA (mDNA) strands from magnetic beads. The separated mDNA was used for hybridization on immobilized cDNA strands on np-Au microelectrode. Upon activatingExo III, cDNA digested into multiple mononucleotides and subsequently the mDNA could be reused to hybridize with extra cDNA. As a result, the increase in the target concentration leads to a decline of the cDNA on the electrode. Finally, the reminded cDNA strands on the np-Au surface with the assistance of help DNA (hDNA), were identified with report DNA/Au-NP containing methylene blue to create the electrochemical signal.

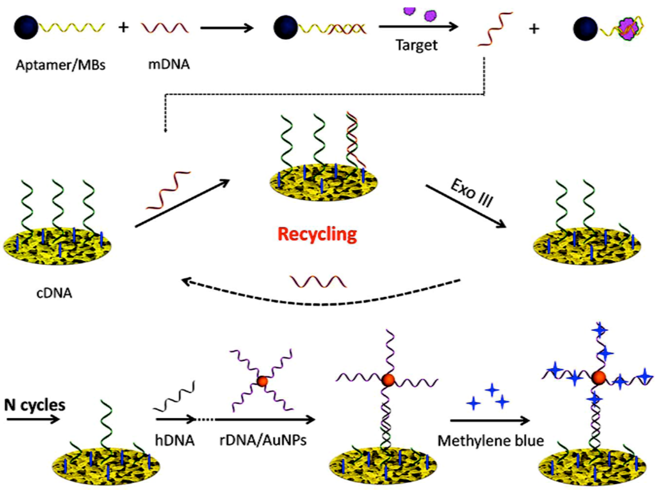

Fig. 7. Schematic representation of the versatile electrochemical aptasensors based on the np Au microelectrode and an Exo III-assisted signal amplification strategy. Reproduced from Ref. [83].

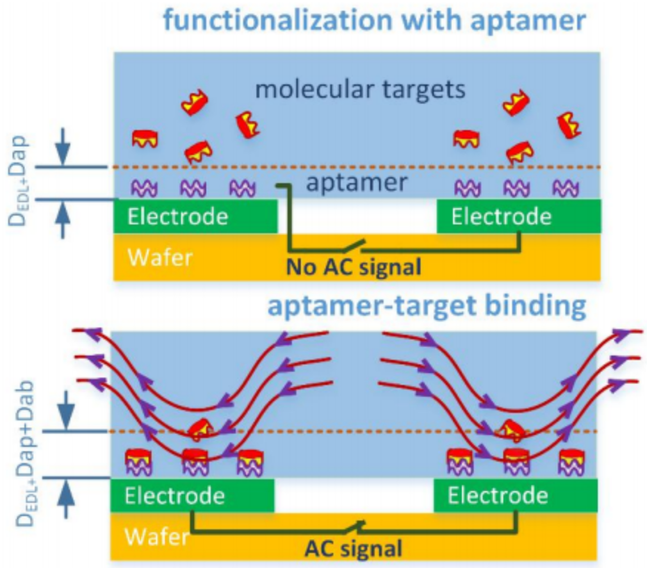

Fig. 8. Changes at the electrode surface due to the binding of specific target to immobilized aptamer. Reproduced from Ref. [79].

1.3.2. Electrochemical aptasensor based on glassy carbon electrode

Taking advantage of AuNPs, a BPA aptasensor was developed using functionalized carbon nanotubes (CNTs) and prussian blue (PB) concisely (AuNPs/PB/CNTs-COOH). In this system, a capture probe (complementary DNA) and a recognition probe (BPA aptamer) were attached to the electrode surface. Conformational restriction occurred after the addition of the target. The deposition of neatly arranged AuNPs and the in situ formation of PB as a label are the advantages of the proposed nanoaptasensor. For this electrochemical platform, two linear ranges were demonstrated; one from 0.1 to 1 pM and the other from 10 pM to 10 nM [89].

In another approach, glassy carbon (GC) electrode modified with acid oxidized carbon nanotubes (CNTs-COOH) to produce CNTs-COOH/GC electrode in order to fabricate a novel signal amplification strategy. Via electrodeposition of the CNTs-COOH/GC electrode with gold-platinum nanoparticles (Au-PtNPs), the Au-PtNPs/CNTs-COOH/GC electrode was produced. In this system acriflavine (ACF) was attached to the electrode surface as a redox probe and through the formation of phosphoramidate bond, BPA-aptamer was joined to ACF [90]. Quantitative detection of BPA was provided by investigating differential pulse voltammetric (DPV) responses of ACF peak before and after formation of BPA-aptamer complexes [90].

In another study, Fe_3O_4/AuNPs/CNTs nanocomposite and amine-terminated BPA-aptamer were immobilized on the surface of GC electrodes through the covalent amide bonds and drop casting with glutaraldehyde as linker [50]. This constructed aptasensor has combined the benefits of deposited Fe_3O_4/AuNPs, the covalent bond of the aptamer at the sensing interface and has potential application in clinic assay. As an illustration, the linear range was found in a wide range from 1 to 600 nM.

Also, in a similar design, (PtNPs/PEI/CNTs-COOH) GC electrode with the covalent bond to an amine-terminated DNA sequence (ssDNA1) was approached to another signal amplification strategy. Also complementary sequence BPA-aptamer (ssDNA2) as detection probe hybridized with the ssDNA1. Upon formation of the BPA/aptamer complex, the electron transfer property of $[Fe(CN)_6]^{-3/-4}$ as the electrochemical indicator was changed.

A label-free electrochemical aptamer-based sensor for BPA detection in milk samples was developed based on AuNPsdotted graphene (AuNPs/GR) nanocomposites film that was modified by glassy carbon electrode (GCE). The aptamer was immobilized on a GCE via the formation of thiol–gold bonds between the AuNPs and thiol terminated aptamers [91]. In this system ferricyanide was used as a probe to investigate the interactions between aptamer and BPA resultingin AuNPs/GR layer presenting a good response for BPA determination that monitored by cyclic voltammetry (CV) and differential pulse voltammetry (DPV). The peak current change (DI) of ferricyanide exhibited a linear range for BPA concentrations from 0.01 µM to 10 µM with the LOD of 5 nM. Also, biocompatibility and conductivity nanostructure of GNPs/GR nanocomposite was characterized by CV, atomic force microscope and scanning electron microscopy. It is worth noting that 30 min was chosen as the BPA detection time. The aptasensorwas used to detect the BPA concentration after keeping a 14-day period in refrigerator (4 °C) and it did not show a significant change in DI (lower than 5%), yet it demonstrated the biosensor has a good stability [91].

For clinical diagnosis, a direct electrochemical detection system was developed by Zhu et al. with aptamer-functionalized nanoporous gold film (NPGF) [92]. In this method, NPGF was attached onto GCE and then functionalized via thiol of aptamer. NPGF acted as the electrochemical catalyst for the redox reaction of BPA and amplified the electrochemical signals of BPA-aptamer complex. Under the optimal experimental conditions the aptasensor has an LOD of 0.056 ± 0.004 nM and linearity obtained from 0.1 nM to 100 nM in human serum samples, with satisfying stability (up to two months) [92].

1.3.3. Electrochemical aptasensor based on boron-doped diamond

Because of the weak electro-activity of BPA and the deposition of oxidation byproducts on the surface of electrodes, low efficiency and repeatability in electrochemical sensors is a common hindrance. So the linearity range in typical electrochemical methods is in 10^{-7}–10^{-11} mol L^{-1}, which is relatively low compared to LC-MS or GC-MS methods [93]. Some of the unique characters of conductive boron-doped diamond (BDD) such as chemical inertness, electrostatic capacity, very low background current, high resistance to fouling and excellent electrochemical stability make it an attractive proposal in order to reduce the LOD of BPA. Owing to proper attribute and high efficiency, BDD has been employed for biosensing applications [93]. The hydrogen terminated BDD electrode was used to display the BPA with a LOD of 2.1×10^{-7} mol L^{-1}, which showed a relative low sensitivity [94]. Modification with tyrosinase result in an increase of LOD down to 1×10^{-11} mol L^{-1} [95]. Accordingly, Ma et al. fabricated an aptasensor based on AuNPs coated BDD modified with aptamers, and 6-mercapto-1-hexanol (MCH) [93].

By means of sputtering method, the BDD film was coated with Au layer and then by a de-wetting process the Au-NPs loaded on BDD substrate (Au-NPs/BDD electrode). After that, the aptamer was immobilized on the AuNPs/BDD through the Au-S bonds. The MCH molecules were absorbed on the electrode surface without aptamer coverage. After immersing the sensor in binding buffer containing target, detection process will be occurred. Records of different BPA concentrations caused the changes in impedance. This approach revealed good linearity rangein the femtomolar scale for trace amounts of target [93].

Furthermore, the BDD surface termination (predominantly hydrogen) may strongly influence the electrochemical activity of this electrode towards redox species and presents a higher electrochemical ability in the oxidation of BPA [94].

1.3.4. Other electrochemical aptasensor

A label-free electrochemical impedimetric sensing strategy was designed for BPA detection in food, drinking water and environment samples [96]. Here, a pentahistidine peptide which conjugated to anti-BPA aptamer was attached to the modified electrode. Because of the close proximity of probe and electrode surface, a highly sensitive system was provided. The specificity and selectivity of this aptasensor was confirmed by two interfering molecules: 4,4′-dihydroxybiphenyl (DHB) and bisphenol P (BPP) [96]. Another rapid sensing method for BPA detection in biological fluids was presented by Lin et al. This work was based on an AC electrokinetics (ACEK) capacitive and aptamer probe that is capable of detecting BPA at femto molar level [97]. ACEK is a sensing technology that utilizes an AC signal over microelectrodes to produce localized fluid motion that facilitates particle enrichment and movement. When the molecules bind to the probes on the surface of electrode, the capacitance of the fluid/electrode interface will change based on the rate of binding, which is measured simultaneously by the same AC signal [98].

Briefly, when a pair of microelectrodes is immersed in electrolyte, the electrode impedance can be as a network of capacitors and resistors, including charge transfer resistance, interfacial capacitors, and electrolyte resistance, as shown in Fig. 8. Electrical double layer (EDL) is an arrangement that observed on the microelectrode surface when it is exposed to a fluid. From the electrical point of view, EDL is a capacitor. When aptamer is adsorbed onto the electrode, the interfacial capacitance (C_{int}) will change because of the change in the surface area and thickness, which can be used to illustrate the deposition of aptamers on the electrodes. After binding BPA to aptamer, sensor surface becomes heavier, and the C_{int} is expected to change to $C_{int,binding}$. The ACEK convection method is able to detect BPA in serum, maternal and cord blood. In addition, this capacitive aptasensor had a LOD of 1.0 fM [97].

A single-step and label-free aptasensor was reported by Cui et al. for the detection of (BPA) in aqueous samples. In this method, aptamer as a probe molecule attached on an aluminum microelectrodes and BPA was quantified by measuring the interfacial capacitance change rate produced by the specific reaction between aptamer and its target [98]. Similar to the previous strategy without AC signal, the target molecules move randomly in the fluid by Brownian motion but the AC signal enforces an ACEK effect to create microfluidic motion for enhanced binding. This ACEK capacitive aptasensor with an LOD less than 10 fM, presented a 20 S response time [98]. One-dimensional (1D) conductive nanomaterials like carbon nanofibers (CNFs) are valuable in sensors, due to ease of modification. employing electrospinning, CNFs can be obtained which offers merits such as cost-effectiveness, efficiency, and reproducibility [99]. Electrospun CNFs are desirable for detection approaches because their structure and electrochemical attribute can be easily controlled by modifying the process conditions.

Accordingly, as a novel design, the field-effect transistor (FET) sensor was reported by Kim et al. base on multichannel carbon nanofibers (MCNFs) modified with BPA-binding aptamers for the detection of BPA. The MCNFs are used as a conductive signal transducer and fabricated via a facile single-nozzle coelectrospinning of two immiscible polymer solutions. Then, the MCNFs are oxidized with a solution of H_2SO_4 and HNO_3 to present carboxyl groups on the fibers surface (Fig. 9). The multichannel structures increase the specific surface area of the transducer. Hence, their interactions between BPA molecules are improved. Via covalent bonding, the carboxyl-functionalized MCNFs located between the amine-functionalized electrode substrate of the FET and amines functionalized BPA-binding aptamers this is led to strong aptamer affinity toward the BPA molecules and therefore provide good electronic performance for aptamer-FET sensor [99]. Hybridization chain reaction (HCR) is a free enzyme and self-assembly process with high amplification ability that can be formed long dsDNA

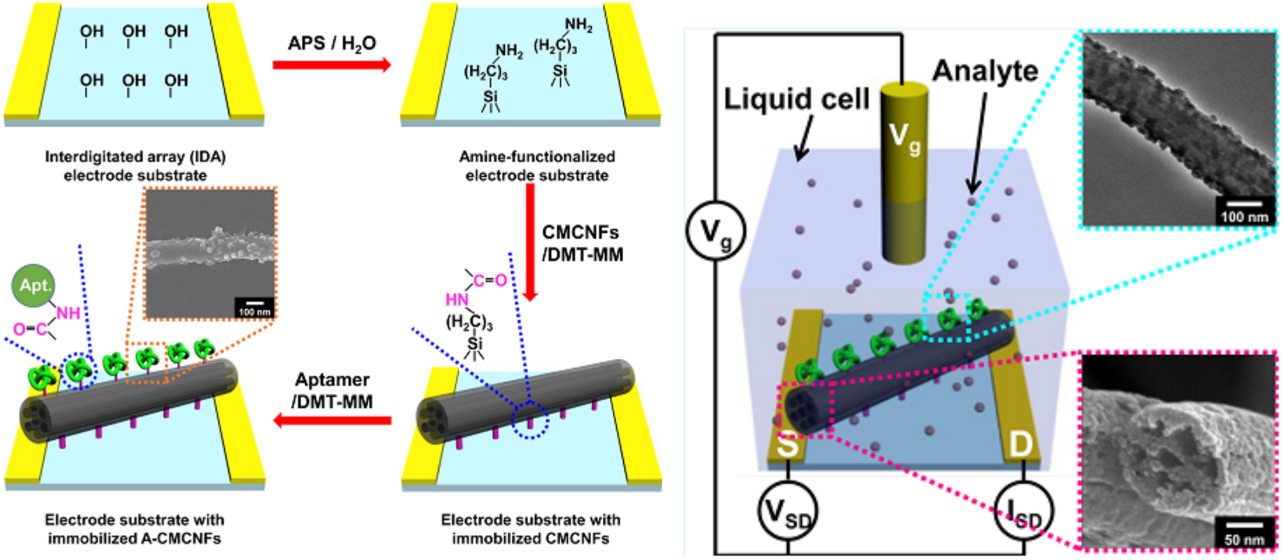

Fig. 9. Schematic diagram showing the immobilization of aptamer-modified CMCNFs (A-CMCNFs) on the electrode. Reproduced from Ref. [84].

through the cascade of hybridization events. The produced dsDNA can be a carrier for the ECL probes like Ru(phen)$_3^{2+}$ to create signal. Based on this strategy, Zhang et al. introduced a new BPA aptasensor [72]. In this method, a capture DNA (CDNA) was modified on the electrode surface and then BPA aptamer was hybridized with CDNA. In the presence of BPA, the CDNA becomes free. Then two hairpin probes react with the free CDNA at the electrode and produce a long chain dsDNA through the HCR reaction. Ru(phen)$_3^{2+}$can be infixed into the dsDNA and relative large ECL intensity can be detected. A highly sensitive PEC aptasensor introduced by Zhang and his co-workers, based on aptamer immobilized TiO_2-Fe_2O_3 NTs. Briefly, with the help of anodic oxidation; these NTs were produced from Ti-Fe foil. In the next step, BPA aptamers were immobilized on TiO_2-Fe_2O_3NTs. In the range of 1.8×10^{-11} to 3.2×10^{-9}, a linear correlation between BPA concentration and photocurrent response was observed. Along with special specificity, the proposed platform achieved LOD of 1.8×10^{-11} [73].

A summary of the reports on BPA aptasensors based on electrochemical methods is listed in Table 3.

1.4. Conclusion and future prospective

Due to endocrine disrupting effects of bisphenol A (BPA) and its serious hazardous effects including cardiovascular problems, reproductive effects, hormone-related cancers and allergic reactions, it is very necessary to establish an efficient and reliable sensing and quantification approach. Till now, various analytical procedures have been introduced for the detection of BPA such as chromatographic and spectroscopic techniques. Although they have good sensitivity, hindrance such as time consuming sample preparation, laborious, required special or expensive equipment limited their application. Hence, validation of simple, sensitive and rapid detection technique seems crucial. In this review, we summarized the recent advances in the development of the aptasensors for sensitive detection of BPA in two basic optical and electrochemical classes.

The colorimetric, fluorescence, SERS and ECL analysis are the technical approaches performed to the construction of the optical based aptasensors with advantages such as small size, ease of operation, high selectivity, and rapid detection with no need for the analytical appliance. In thesetype of sensors, interaction between small molecules and their aptamers could have an effect on the charge-carrier density. So they provide high sensitive and on-site detection ability with desirable effects for BPA. For instance, colorimetric based aptasensors are able to provide target monitoring with naked eyes, which typically employ the salt-induced aggregation of the AuNPs and are considered as the easiest sensing technique without the need for the intercalating dyes and the fluorescent labels. Among the optical approaches for BPA detection, a fluorescence based aptasensor can be impressive to design with the detection limit of 5.4×10^{-17} mol L^{-1}.Compared to optical-based aptasensors, electrochemical aptamer-based sensors are specially popular because of their features such as experimental simplicity and low cost. Among the electrochemical-based aptasensors, the impedance spectroscopy (EIS) is able to determine the BPA trace as slow as 7.2×10^{-15} mol L^{-1}. Also, ECL and cyclic voltammetry techniques have good sufficiency to construct the high sensitive BPA aptasensors. Generally, the electrochemical-based aptasensors exhibit the lower LOD for BPA, which proves the higher ability to detect BPA than optical ones.

The affinity of BPA aptamer when immobilized on the nanomaterials surfaces or conjugated whit fluorophores can be significantly affected by the spacer size, support surface change and the orientation of the conjugate. So, label-free and non-immobilized aptasensors are more efficient and more preferable. For the fabrication of highly sensitive aptasensors for BPA, signal amplification strategy developed through combining different NPs, such Au-PtNPs/CNTs, which reduces the need for aptamer and other compounds, and provides the large signal to noise ratio and high sensitivity in trace concentration. Therefore combinatory techniques cause the most effective detection systems because unique properties of several NPs can be used simultaneously. However, there are some drawbacks in combining strategies including complicated conjugation process and high cost.

Another rational parameter which is a cost effective and important property is related to regenerability and stability of BPA sensor. Although after several configuration and denaturation, the recycling of the original DNA probe will be difficult, the improvement of more reusable aptasensors becomes the challenge required for solving in the future. The conclusion depends on the condition and research goal of the scientist, different BPA aptasensing methods have been selected. Fluorescent and electrochemical based aptasensors for high sensitive purpose as well as colorimetric and lateral flow strip-based sensors for easy and rapid detection are useful. Beside the remarkable advancement in aptasensing of pollutants, some drawbacks are still problematic. For example, factors such as ionic strength, temperature, and pH may affect optimal aptasensor performance. So, it is important to resolve these problems in the future.

Table 3
Electrochemical-based aptasensors for BPA detection.

Detection method	Strategy	Limit of detection (LOD)	Linear range (LR)	Sequence	Advent	disadvent	Ref
Cyclic voltammetry (CV), Impedance Spectroscopy (EIS) and Square Wave Voltammetry (SWV)	Poly(Pyrrole-Nitrilotriacetic Acid)-Aptamer Film	10^{-11} mol L^{-1}	10^{-11} to 10^{-6} mol L^{-1}	(5′X GGG CCG TTC GAA CAC GAG CAT GCC GGT GGG TGG TCA GGT GGGATA GCG TTC CGC GTA TGG CCC AGC GCA TCACGG GTT CGC ACC AGG ACA GTA CTC AGG TCA TCC TAG3′; X = diol)	• highly sensitive and lable free sensing system • Suitable for target detection in food, drinking water and environment samples • Appropriate detection limit	• Time-consuming of the aptasensor and Electrodes preparation • Inappropriate for on-site detection	[97]
AC electrokinetics (ACEK)	The proposed system was fabricated by benchtop equipment and low-cost materials through printed circuit board technique	152.93 aM	1 fM to 10 pM	5′ -CCG GTG GGT GGTCAG GTG GGATAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GCA CCA-3′	• A,high sensitive and rapid biosensing assay(in 20 s) • label-free and single step detection of (BPA) • low-cost capacitive affinity biosensor • exhibits a large linear range • suitable to test BPA in canned food • simple and rapid fabrication process of biosensor	•	[98]
Impedimetric	By means of functionalized carbon nanotubes and prussian blue as labels	0.045 pM	0.1 pM–1 pM 10 pM–10 nM	5′-CCG GTG GGT GGT CAG GTG GGA TAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GC A CCA-3′	• A facile and sensitive detection system with acceptable selectivity • in situ formation of sensor label • covalent bond of the capture probe to the surface of the electrode	• Time-consuming of the AuNPs preparation • Low Stability of AuNPs • Synthesized • Time-consuming of the preparation of nanocomposite • Need for mild condition to achieve impressive functionality	[90]
SWV	Triple-signaling strategy	0.19 pM	1 pM to 100 pM	5′-SH-(CH2)6-CCG GTGGGTGGTCAGG TGGGATAGCGTTCC GCGTATGGCCCA GCG CATCACGG GTTCGCACCA-ferrocene-3′	• A sensing approach with high specificity and sensitivity with good Linear range • Suitable food safety monitoring, bioanalysis and environmental analysis • coupling dual-signaling strategy and the inherent redox activity of target, • Easily extended to detect other redox targets by changing the specific aptamers	• Simultaneous use of two labels in the biosensor • Requiring time about 20 h for the electrode preparation • Need 3 h for the incubation time	[84]
CV	Rely on AuNPs dotted Graphene modified glassy carbon electrode	5 nM	0.01 µM to 10 µM	• 5′-SH-(CH2)6-CCG GTG G GT GGT CAG GTG GGA TAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GC A CCA-3′	• high sensitive, rapid, low cost and label-free aptasensor • The highly conductive and biocompatible nanostructure of GNPs/GR nanocomposite • Exhibiting an excellent performance to determine BPA in milk products • Covalent bond between aptamer and AuNP • Good stability of the aptasensor (in refrigerator (4 _C) for 2 weeks)	• Time-consuming of nanocomposite constraction and aptamer immobilization on the surface of the Au electrode	[92]
CV	signal amplification strategy with Exo III on a nanoporous gold microelectrode	43 pM	16.87 pM to 8.76 nM	ND	• Having large potential to detect other antibiotics by using the appropriate aptamers • Use of nanoporous gold microelectrode with 3D nanoporous structures, large specific area, high stability and clean surface • Wide linear ranges • Signal amplification strategy	• Enzyme-dependent method • Need for more DNA in the identification process	[89]

(*continued on next page*)

Table 3 (*continued*)

Detection method	Strategy	Limit of detection (LOD)	Linear range (LR)	Sequence	Advent	disadvent	Ref
EIS	Aptamer sandwich-based carbon nanotube sensor technique	1 pM	ND	ND	• highly selective and sensitive detection approach for small non-polar pollutant molecules • Facilitate electrode construction • having variety performance such as food safety, medical diagnostics and environmental control • disulfide bonding between aptamers and Au electrodes	• Use more aptamer in the sensor	[83]
CV, EIS and differential pulse voltammetry (DPV)	Electrodeposition of gold-platinum nanoparticles on modified glassy carbon (GC) electrode	0.035 pM	0.100–1.00 pM 10.0 pM–700 mM	5′-CCG GTG GGT GGT CAG GTG GGA TAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GCA CCA-3′	• a signal amplification strategy • covalent bond of the redox probe to the surface of the electrode • covalent bond between the aptamer and redox probe	aptasensor • Need to The EIS measurement performed in the presence of 0.1 M PBS containing 5.0 mM [Fe(CN) 6]3/4 • Low-term stability of modified electrode(for 8 days at 4 C)	[91]
CV, EIS, DPV	Aptamer functionalized nanoporous gold film (NPGF)	0.056 nM	0.1 nM to 100 nM	5-CCG GTG GGT GGT CAG GTG GGATAG CGT TCC GCGTAT GGC CCA GCG CAT CAC GGGTTC GCA CCA-3′	• direct electrochemical detection of BPA • Au-S bond of aptamer on the sensor • Providing new opportunities for clinical diagnosis of BPA (human serum samples) • satisfying stability of the fabricated sensor (two months)	• Physical attach of NPG onto the GCE surface • Time-consuming of the preparation of aptasensor (about 2 days) • Need for moderate condition to obtain • effective functionality (pH 7.5)	[93]
CV, EIS, DPV	Deposition of platinum nanoparticles on polyethyleneimine-functionalized carbon nanotubes	210 pM	1–400 nM	5′-CCG GTG G GT GGT CAG GTG GGA TAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GC A CCA-3′	• use of acriflavine as aredox probe in biosensore • signal amplification strategy • covalently immobilized probe at the surface of sensore • a label-free electrochemical aptasensor •wide linear response range	• Time-consuming of the constraction of ACF/Au-PtNPs/CNTs-COOH electrode	[101]
EIS	Boron-doped diamond electrode coated with Au-NPs, aptamers, and 6-mercapto-1-hexanol (MCH)	7.2×10^{-15} mol L^{-1}	1.0×10^{-14} to 1.0×10^{-9} mol L^{-1}	5′-SH-(CH2)6-CCG GTG GGT GGT CAG GTG GGA TAG CGT TCC GCG TATGGC CCA GCG CAT CAC GGG TTC GCA CCA-3′	• Using the conductive boron-doped diamond with unique characters like wide potential window, good mechanical stability • the Au-S bond between the electrode and aptamer • The highly selective and sensitive detection and suitable for trace detecting with femtomolar detection limit • Suitable for target detection in milk products • and high resistance to fouling	• Time-consuming of the preparation of electrode • Need for high temperature (800 oC) to fabricate electrode	[95]
CV, EIS, DPV	Fe_3O_4/AuNPs)-decorated carbon nanotubes (CNTs)	300 pM	1 to 600 nM	5′-CCG GTG GGT GGT CAG GTG GGA TAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GCA CCA-3′	• a label-free electrochemical aptasensor • covalent attachment of the detection probe at the surface of sensore • broad potential application in clinic assay	• Time-consuming of the Preparation of the nanocomposite • low stability of the aptasensore	[51]

(*continued on next page*)

Table 3 (*continued*)

Detection method	Strategy	Limit of detection (LOD)	Linear range (LR)	Sequence	Advent	disadvent	Ref
CV, EIS	nontarget-induced extension of aptamer length triggered by TdT and complementary strand	15 pM	0.08–15 nM	5′Thiol CCGGTGGGTGGTCAGGTGGGATAGCGTTCCGC GTATGGCCCAGCGCATCACGGGTTCGCACCA-3′	• suitable for Tap water and juice samples • label free and high specificity of aptasensore • can be applied to the sensing of other contaminants	• Increased costs due to the need for enzymes	[86]
Capacitance sensing system	Rely on an aptamer probe and AC electrokinetics capacitive sensing technique	1.0 fM	1 fM–10 pM	5′ -CCG GTG GGT GGTCAG GTG GGA TAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GCA CCA-3′	• A label-free aptasensore • acceptable sensitivity (10 pM) with wide linear range • rapid detection of BPA (30 s) with low LOD • beneficial for ultra-trace sensing • Detection of BPA in biological fluids		[99]
CV, EIS	microfluid integrated electrochemical sensor	2×10^{-13} M	5×10^{-12} to 1×10^{-9} M	ND	• Easy to use, long term response time • High sensitivity of the aptasensor • Wide linear dynamic range • Rapid detection of BPA	• Time-consuming and cost of construction of nano-structured gold electrode	[85]
FET	Field-effect transistor (FET) sensor employing aptamer modified multichannel carbon nanofibers (MCNFs)	1 fM	ND	5′-NH2-(CH2)6-CCG GTG GGT GGT CAG GTG GGA TAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GCA CCA- 3′	• Exhibiting an excellent performance to determine BPA in trace amounts • reusable sensors for repeated assays • Satisfactory stability of the sensor (4 weeks).	• Time-consuming of fabrication of Carboxyl-Functionalized MCNFs. • requires high temperatures and inert atmospheres during fabrication of MCNFs • Requiring time about 12 h for the aptasensor preparation	[100]
Capacitive	Aptamer modified disposable electrode	10 fM	10 fM–10 pM	5′-CCG GTG GGT GGTCAG GTG GGA TAG CGT TCC GCG TAT GGC CCA GCG CAT CAC GGG TTC GCA CCA-3′.	• A label-free and single-step method • Very sensitive detection of BPA with a 20 s response time • Use of Low-cost commercially available microelectrodes • Quick and easy construction of aptasensor • Detection of BPA in human serum samples	•	[85]

Declaration of Competing Interest

We declare there is no conflict of interest about this article.

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