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Nanomaterial-based aptasensors and bioaffinity sensors for quantitative detection of 17β-estradiol

Alireza Nezami [a, c], Rahim Nosrati [b, c], Behrouz Golichenari [b, c], Ramin Rezaee [d], Georgios I. Chatzidakis [e], Aristides M. Tsatsakis [e], Gholamreza Karimi [a, *]

[a] Pharmaceutical Research Center, Pharmacy School, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Department of Pharmaceutical Biotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[c] Biotechnology Research Center, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran
[d] Clinical Research Unit, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[e] Department of Forensic Sciences and Toxicology, Faculty of Medicine, University of Crete, Heraklion 71003, Greece

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ABSTRACT

One of the most important endogenous estrogens is 17β-estradiol, which disturbed the endocrine system, and causing adverse effects on the growth, reproduction and development of the body. It is necessary to develop a convenient and rapid analytical method to detect estradiol with high sensitivity and selectivity. For determination of 17β-estradiol, methods such as high performance liquid chromatography/mass spectrometry and gas chromatography/mass spectrometry were used. However, these methods often need expensive instruments, complex pretreatment, large volumes of harmful solvents and professional operation. Aptamers have been used as a new biosensor platform for detection of 17β-estradiol in different samples. This article provides an overview of the applications of aptasensors in analysis and monitoring of 17β-estradiol. After a brief description of the steroids, recent advances and applications of aptamer-based biosensors are presented. We have paid attention to the potential role of bioaffinity systems in the detection and quantitative determination of 17β-estradiol.

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1. Introduction

Steroids are naturally found in animals, microorganisms and plants and possess a construction of three cyclohexane carbon rings in companion with one pentagonal carbon ring (arranged in a 6–6–6–5 structure), which is attached to various functional groups and side chains. All steroidal compounds derived from cholesterol. Some examples of steroid hormones and their source compound are shown in Table 1. Estrone (E1), 17β-estradiol (E2) and estriol (E3) (main natural estrogens) are C18 steroids that have different oxidation state of their rings. These compounds induce female secondary sexual characteristics and reproductive structures. Moreover, mestranol (MES) or ethinylestradiol (EE2) are synthetic estrogens that are derived from estradiol. Estrogens have been used in animal fattening because of their anabolic effects [1].

One of the most important environmental endogenous estrogens is 17β-estradiol (E2), which is disturbed in the endocrine system, and can cause adverse effects on the growth, reproduction and development of the body and endanger the offspring health [2]. 17β-Estradiol has the strongest estrogen effect when it enters the organism [3]. This entrance can lead to immunological diseases, gender imbalance at birth and reproductive system diseases, etc. [4–9]. Water samples with content of estradiol have been reported by numerous studies [10–14]. Dairy farms, aquaculture facilities, and surface waters with actively spawning fish are the most important sources of environmental pollution. The investigation results indicated that dairy wastes contain up to 650 ng L^{-1} of endogenous estrogens 17β-estradiol, estrone, androgens testosterone and androstenedione. These hormones have been also found around 1 mg L^{-1} in nearby groundwater, nearby surface waters and tile drain likely impacted by animal wastes. Samples from rivers containing spawning adult Chinook salmon have been similar concentrations. Detectable concentrations of steroid hormones in these sources can cause adverse effect on human and other animals because of accumulation capacity [15]. When E2 in water reaches 10–12 mol L^{-1} [16–18], male fish may be feminized [19]. Afterward humans would be greatly affected due to bioaccumulation through food chain even at low concentration of estradiol. In this way, the effect of low dose 17β-estradiol on bone turnover, sex hormone levels, and side effects in older women were studied. According to

* Corresponding author.
E-mail address: karimig@mums.ac.ir (G. Karimi).

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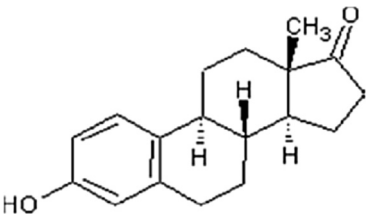
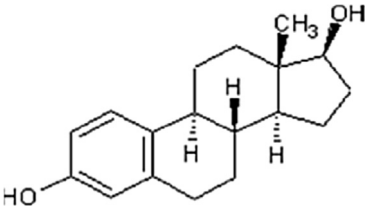
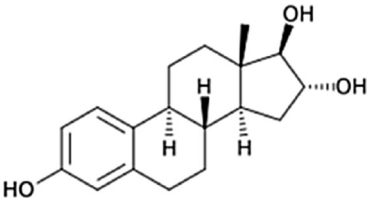
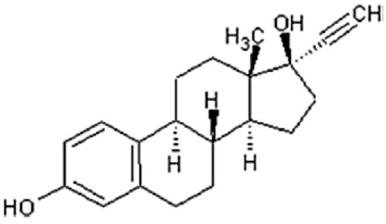
Table 1
Chemical structures and properties of some estrogens.

Name	Systematic name	Synthetic/natural (S)/(N)	Summary structure	Structure
Estrone (E1)	Estra-1,3,5(10) trien-17-one	N	$C_{18}H_{22}O_2$	
17β-estradiol (E2)	Estra-1,3,5(10)-triene-3,17diol	N	$C_{18}H_{24}O_2$	
Estriol (E3)	(16-alpha, 17-beta)estra 1,3,5(10)-triene-3,16,17 triol	N	$C_{18}H_{24}O_3$	
Ethynylestradiol (EE2)	19-norpregna 1,3,5(10)-triene 20-yn-3,17-diol	S	$C_{20}H_{24}O_2$	

the results, low dose of estrogen (0.25 mg/day) lead to reduced bone turnover, increased E2 and estrone levels and increased side effects [20]. Hence, it is necessary to develop a convenient and rapid analytical method for characterization of estradiol with high sensitivity and selectivity to control public and environmental health [10].

Common methods such as HPLC/MS [21], GC/MS [22] and HPLC [23] analysis are sensitive and selective techniques in determination of estradiol; however, these, often need expensive instrumentations, complex pretreatment, usage of large volumes of harmful solvents and professional operation [24]. In the past decade, several biosensors have been established for monitoring and management of 17β-estradiol [25,26]. These biosensors can detect estrogenic compounds, such as 17β-estradiol with notable sensitivity, despite the fact that their specificity is compromised raised from their high affinity to other xenoendocrines and lack of specificity [27,28]. Recently, nanobiosensors and immunosensors have also been broadly used for rapid and sensitive detection of 17β-estradiol along utilizing antibodies or functional polymers.

Among afore-mentioned developed detection strategies, aptamer-based biosensors have attracted considerable attention due to their objectivity that can prepare a specific, sensitive, portable and simple set up for detection [29,30]. Aptamers are short RNA or DNA fragments capable of binding to target molecules with high affinity and specificity [31,32]. The three-dimensional (3D) stability of aptamers offers feasibility in different conditions, which may not be presented by antibody based biosensors. In this article, we pay deep attention to the recent advances in DNA-based aptasensors developed for 17β-estradiol detection. DNA aptamers have some advantage to RNA aptamers. DNA aptamers are easier to handle and identify and more stable than RNA aptamers. The first report of specific DNA aptamer binding to 17β-estradiol, which was selected by the SELEX process, was presented by Kim et al. The selected DNA aptamer probe used in their study was: 5′-Biotin GCTTCCAGCTTATTGAATTACACGCAGAGGGTAGCGGCTCTGCGCATT-CAATGCTGCGCGCTGAAGCGCGGAAGC-3′. This DNA strand was 76-mer and 23 kDa [33]. In other studies, generally same probe is used and some modification employed to increase affinity to 17β-estradiol. Various methods and different approach, such as aptamer modification, as well use of Au and/or other nanoparticles, result in different affinity, accuracy, sensitivity and selectivity. The present review discussed about these methods in the following sections. We classified 17β-estradiol DNA-based aptasensors according to their signal-harvesting methods, including optical and electrochemical approaches.

A summary of the reports on 17β-estradiol aptasensors based on electrochemical and optical methods are provided in Table 2.

2. Aptamer-based 17β-estradiol biosensors

A biosensor provides selective quantitative or semi-quantitative measurement of an analyte by incorporating a biological

Table 2
17β-Estradiol aptasensors based on electrochemical and optical methods.

Type of sensor	Detection methods	Strategy	LOD	Linear range	References
Aptamer-based	Fluorescence	Aptamer-based folding fluorescent sensor	2.1 nM	Not reported	[4]
		Fluorescence resonance energy transfer (FRET)	0.22 nM	0.82–20.5 nM	[42]
		Label-free fluorescent aptasensor based	37 nM	0.08–0.4 μM	[43]
	Colorimetry	Colorimetric-based aptamers immobilized on unmodified Au NPs	0.1 ng mL^{-1}	4.5×10^{-7} to 7.5×10^{-7} M	[37]
		DNA aptamer-coated AuNPs	200 pM	200–800 pM	[50]
	Electrochemiluminescence	Label-free competitive electrochemiluminescence (ECL)	1.1×10^{-12} mol L^{-1}	0.01–10 nmol L^{-1}	[52]
	Spectroelectrochemical	Spectroelectrochemical dynamics of dendritic polythiophene star copolymer aptameric biosensor	Not reported	0.1–100 nM	[60]
	Electrochemical	Electrochemical using DNA aptamer immobilized Au electrode chip	0.1 nM	Not reported	[33]
		Electrochemical aptasensor constructed on hierarchical dendritic Au/BDD electrode	5×10^{-15} mol/L	1×10^{-14} to 1×10^{-9} mol/L	[39]
		Glassy carbon electrode modified with copper sulfide nanosheets and Au NPs, and applying enzyme based signal amplification	6×10^{-14} M	5×10^{-13} to 5×10^{-9} M	[62]
		Label-free electrochemical aptasensor	1×10^{-15} M	1×10^{-15} to 1×10^{-6} M	[63]
		Label-free aptasensor based on NiHCNFe NPs as signal probe	0.8×10^{-12} M	1×10^{-12} to 6×10^{-10} M	[65]
		Carbon nanotube field effect transistor aptasensors (CNT FETs)	5×10^{-8} M	5×10^{-8} to 1.6×10^{-6} M	[66]
		Aptamer/Au nanoparticles/cobalt sulfide nanosheets	7.0×10^{-13} M	1×10^{-9} to 1×10^{-12} M	[67]
		Size-controllable ultrathin carboxylated polypyrrole nanotube transducer	1 fM	Not reported	[68]
	Photoelectrochemical	Photoelectrochemical aptasensor	33 fM	0.05–15 pM	[40]
		α-Fe_2O_3-NG-AuNRs hybrids as photoactive materials and aptamer as recognition element	3.3 × 10–16 M	1×10^{-15} M to 1×10^{-9} M	[73]
Molecularly imprinted polymers (MIPs)	Electrochemical	Molecularly imprinted polymeric microspheres and multi-walled carbon nanotubes grafted with Au NPs	2.5×10^{-16} M	1×10^{-15} to 1×10^{-6} M	[69]
Bioaffinity sensors	Optical	Estrogen receptor (ER) binding assay of chemicals with a SPR	4.04×10^{-10} M	Not reported	[75]
	Fluorescence	FRET-based biosensor	7×10^{-8} M	Not reported	[78]
	Electrochemical	Lipid bilayers modified by Au NPs	1 ng/L	5–150 ng/L	[80]

recognition element with a signal conversion unit (a transducer). Aptasensors are biosensors in which aptamers serve as bio-recognition element [34–36]. Aptasensor-based systems equipped with different detection methods including, fluorescence [4], colorimetry [37], electrochemistry [38,39] and photo-electrochemical (PEC) [40] have been developed.

2.1. Optical-based 17β-estradiol aptasensors

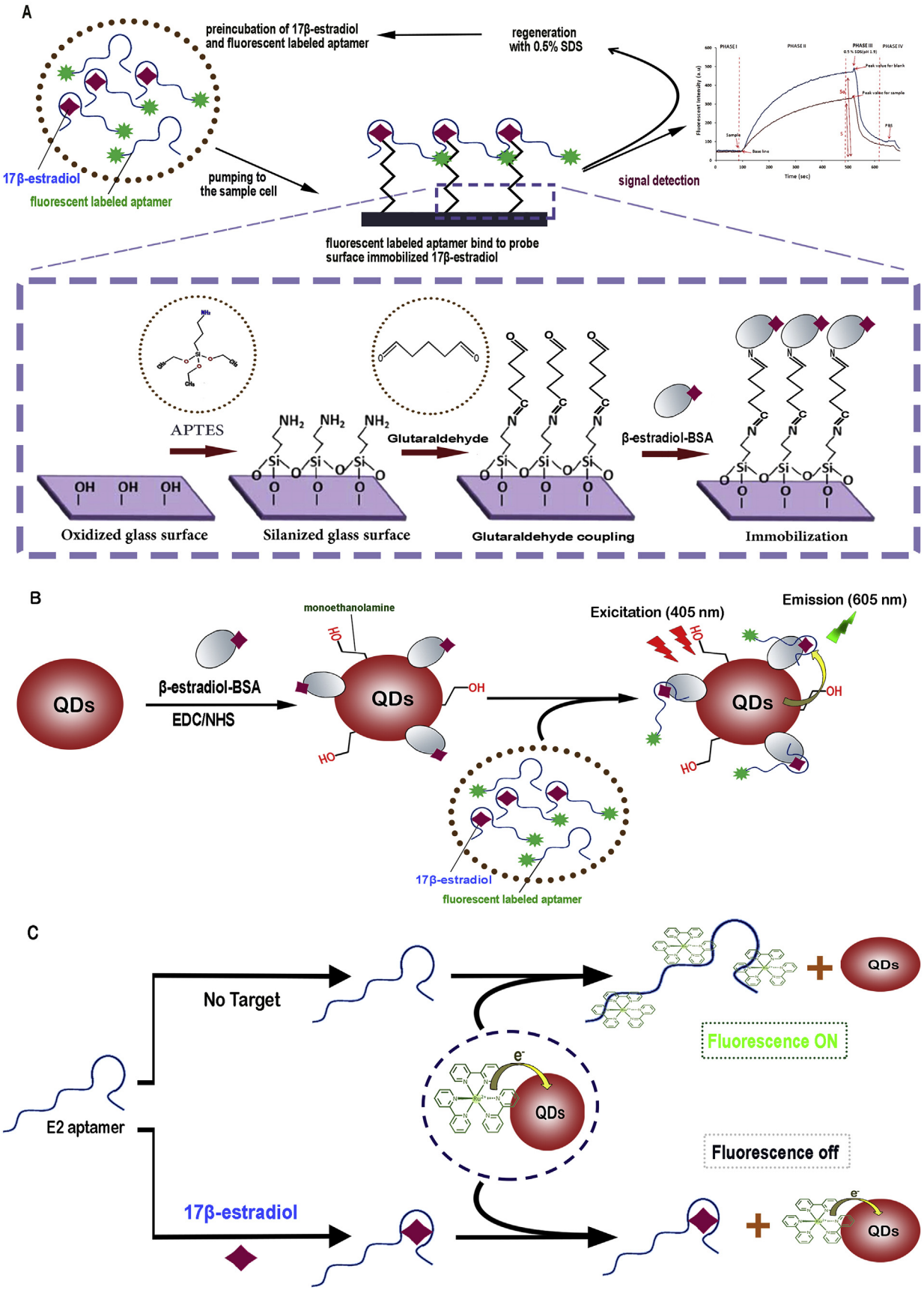
The combination of aptamers, as the recognition part with different optical analytical methods as the signal transductions, results optical aptasensors. Optical analyses because of relatively easy, quick and high sensitivity are widely used in production of aptasensors. Optical aptasensors are divided into five main groups, namely, fluorescence, colorimetry, chemiluminescence (CL), surface-enhanced Raman scattering (SERS) and surface plasmon resonance (SPR) [41]. In this section, we summarized optical aptasensors for 17β-estradiol detection based on fluorescence, colorimetry and electrochemiluminescence transducing techniques.

2.1.1. Fluorescence-based 17β-estradiol aptasensors

Fluorescence as one of the most common optical methods could be routinely employed in the development of aptasensors, due to its prominent characteristics including high efficiency and sensitivity. Fluorescence-based aptasensors are mainly divided into labeled and label-free ones [41]. Briefly, when aptamer conformation is changed, recognition events between target molecules and aptamers occur. Conformational modification may be used for changing the local environment of nanomaterials or fluorophores, and accordingly, modifying the emission properties of fluorescent systems. Fluorescent methods can be used for determination of bio-interactions in aqueous environment due to the flexible ways in quantitative analysis with a wide response range and high sensitivity. Optical-based aptasensors routinely used FRET (fluorescence resonance energy transfer) phenomenon which depend on the energy transition between two fluorescent molecules—donor and acceptor.

Based on these properties, Yildirim et al. developed a high-affinity DNA aptamer for 17β-estradiol. In this platform, samples containing various concentrations of 17β-estradiol were mixed with a known concentration of fluorescent-labeled DNA aptamer. The capture molecular, β-estradiol 6-(O-carboxy-methyl) oxime-BSA, was covalently immobilized onto the optical fiber sensor surface with an indirect competitive detection mode. Then, sample admixture was pumped to the sensor surface and a higher concentration of 17β-estradiol caused less fluorescence-labeled aptamer bound to the sensor surface and weaker fluorescence signal (Fig. 1A). The detection limit (LOD) was 2.1 nM (0.6 ng mL^{-1}). The sensor regenerated with a 0.5% SDS solution (pH 1.9) and the sensor surface was reused for more than hundreds of measurements during the 4-months testing period of this study without significant reduction of the sensor performance. This system can be applied for on-site real-time inexpensive and user-friendly monitoring of 17β-estradiol in environmental samples such as effluents or waste water [4].

A unique FRET-based aptasensors was reported by Long et al. for detection of E2 (Fig. 1B). Their manner was based on incubation of quantum dot (QD) nano-bioprobe as donor, the fluorescence-


A
preincubation of 17β-estradiol and fluorescent labeled aptamer
regeneration with 0.5% SDS
17β-estradiol
fluorescent labeled aptamer
pumping to the sample cell
signal detection
fluorescent labeled aptamer bind to probe surface immobilized 17β-estradiol
APTES
Glutaraldehyde
β-estradiol-BSA
Oxidized glass surface
Silanized glass surface
Glutaraldehyde coupling
Immobilization
B
QDs
β-estradiol-BSA
EDC/NHS
monoethanolamine
Excitation (405 nm)
Emission (605 nm)
17β-estradiol
fluorescent labeled aptamer
C
No Target
E2 aptamer
17β-estradiol
Fluorescence ON
Fluorescence off
QDs

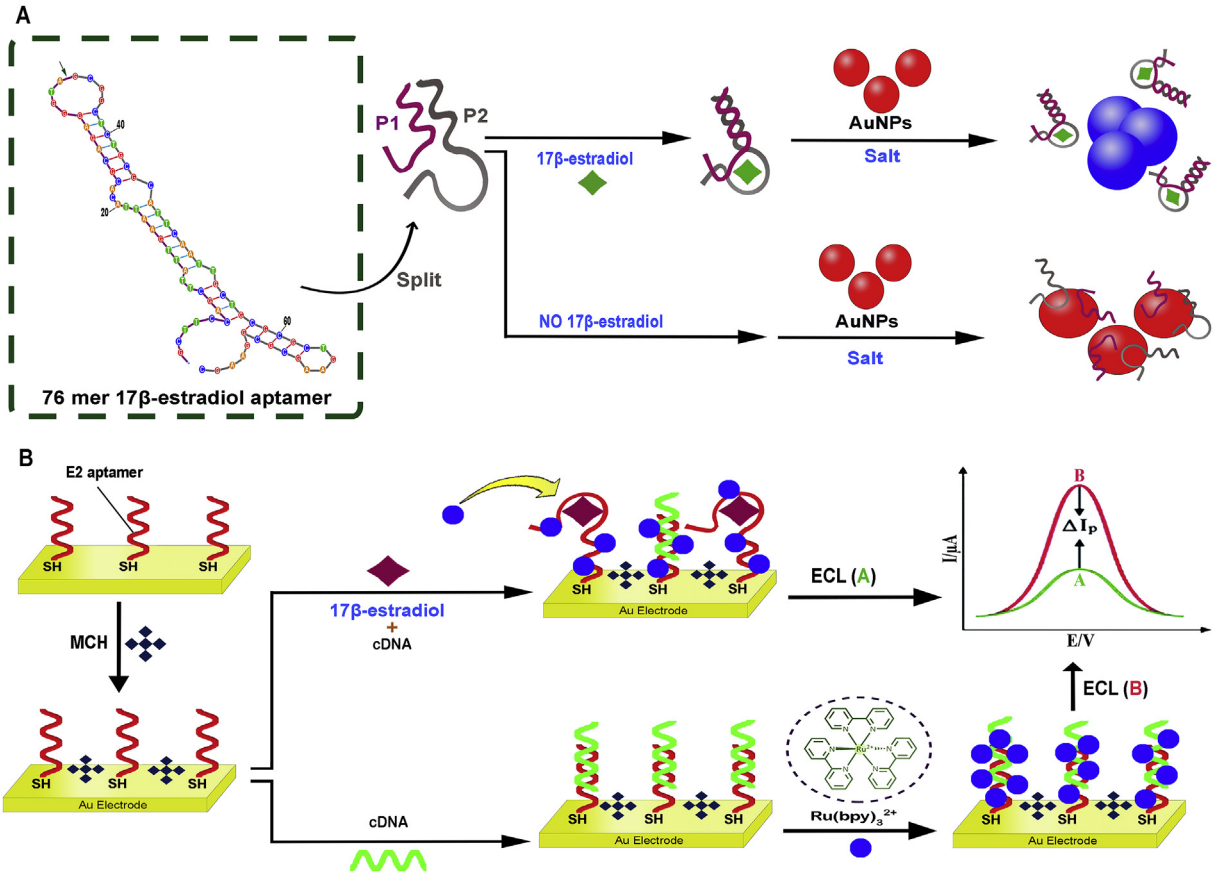


Fig. 2. (A) Colorimetric aptasensors proposed for E2 determination based on split DNA aptamers immobilized on unmodified Au-NPs. The 76-mer specific aptamer has been considered the mainstay in development of electrochemical aptasensors in the tracing E2 [53]. (B) General scheme for the determination of E2 by means of label-free and sensitive chemiluminescence aptasensor.
Adapted from published papers [34,48].

labeled DNA aptamer and E2 various concentration. A higher 17β-estradiol concentration led to lower fluorescence signal because fewer fluorescence-labeled DNA aptamers bound to the QD surface. The concentration range of the sensor was 0.82–20.5 nM with a limit of detection of 0.22 nM. QD nano-bioprobe can stored in a refrigerator at 4°C for 45 days with <10% reduction in the average maximum signal response. The result showed the ability of the sensor to discriminate structurally similar molecules from each other [42].

In a similar manner, Huang et al. developed another sensitive and specific FRET based on QD-ruthenium (Ru) complex for E2 determination (Fig. 1C). Ru complex (the fluorescence quenchers of QDs), preferred to bind with aptamer and lead to the fluorescence rise of QDs. In the optimal condition, the fluorescence intensity was linearly proportional to the concentration of E2 with a LOD 37 nM and concentration range of the sensor was 0.08–0.4 μM. Qualitative determination without complex instruments was available by naked eyes [43]. Recently, Bai et al. used 76-mer E2 aptamer for 19-nortestosterone (NT) detection. The sensor exhibited a detection limit of 5 μM with a wide dynamic range (5–1000 μM). They split the 76-mer aptamer into two moieties (P1 and P2); P1 was labeled with a quencher (BHQ) and P2 with a fluorophore (6FAM). P1 and P2 were employed to detect NT via FRET quenching in a homogeneous solution [44]. Recently, a fluorescent aptasensor for E2 determination in aqueous solution developed by using label-free E2-specific aptamer and AuNPs quenching the fluorescence of Rhodamine B as fluorescent indicator [45].

2.1.2. *Colorimetric-based 17β-estradiol aptasensors*

Colorimetric assay has been widely used in consequence of its low cost, practicality, simplicity and the possibility of monitoring the color change by the naked eyes [46]. Gold and silver nanoparticles are perfect candidates for colorimetric assays because of the simplicity, high sensitivity, potential for high-throughput analysis and size/distance-dependent optical properties [47–49].

In view of such properties, Liu et al. designed colorimetric detection of 17β-estradiol using split DNA aptamers immobilized on unmodified gold nanoparticles (Au-NPs) (Fig. 2A). They split the 76-mer E2 aptamer into two short pieces to improve the AuNP-based colorimetric sensitivity. The results showed that the split P1 + P2 still retained the original 76-mer aptamer's affinity and specificity, but increased the LOD by 10-fold, indicating 17β-estradiol at concentrations as low as 0.1 ng mL^{-1} could be traced with linear range (LR) from 450 to 750 nM. The increased sensitivity may be due to lower affinity to the AuNPs and lower adsorbed aptamer concentration of a short single-strand DNA (ssDNA) sequence. This study provided a new method using long-sequence modified aptamers to develop a highly sensitive AuNP-based colorimetric aptasensor [37].

Fig. 1. Some of the designed fluorescence-based aptasensors and their sensing mechanism for 17β-estradiol detection.
Adapted from published papers [4,39,41].

In 2015, Alsager et al. developed an ultrasensitive colorimetric strategy for detection of E2 using DNA aptamer-coated AuNPs. To implement this, two specific 35 and 22-mer aptamers were designed based on deletion of flanking nucleotides on either side of the inner core from 76-mer aptamer sequences. This modify caused target-bound aptamers remain adhered to AuNPs which results suppressing in signal transduction. 22-mer aptamer improved differentiation against other steroidal molecules and colorimetric sensitivity for E2 detection by 25-fold compared with the 75-mer from 5 nM to 200 pM. Linear response was observed between 200 and 800 pM. The comparative examination of sensitivity with this method showed good differentiation against the bisphenol A; however, testosterone triggered a 33% and progesterone a 45% response relative to E2; respectively [50].

2.1.3. Electrochemiluminescence-based 17β-estradiol aptasensors

Chemiluminescence assay is highly sensitive, cost-effective devices with a wide linear range of detection [51]. In this aspect, Zhang and co-workers investigated a label-free competitive electrochemiluminescence (ECL) aptasensor for the determination of E2 (Fig. 2B). For detection probe to bind with any unbound E2 aptamer, a complementary DNA (cDNA) was designed. ECL indicator was Tris(2,20-bipyridyl)ruthenium(II) ($Ru(bpy)_3^{2+}$) which electrostatically bound to the E2 aptamer; it competes with the cDNA for aptamer binding sites. When E2 concentration is low, content of cDNA can bind to the E2 aptamer increased and adsorb more $Ru(bpy)_3^{2+}$, which lead to enhancing the ECL intensity. The aptamer capture E2 lead to bind less cDNA with an accompanying decrease in $Ru(bpy)_3^{2+}$ and a decrease in ECL intensity in presence more E2. This assay possesses a widely LR from 0.01 to 10 nmol L^{-1} with a LOD of 1.1×10^{-12} mol L^{-1}. Recoveries of this protocol in human serum, human urine, and tap water samples were 89.8–100.0%, 90.0–103.5% and 89.5–95.0%, respectively [52].

2.2. Electrochemical-based 17β-estradiol aptasensors

Electrochemical biosensors, a device which a biological material is paired with an electrode transducer, due to their unique properties, such as rapid response, simplicity, and low-cost detection are interesting [53,54]. General scheme of an electrochemical biosensor consists of sensing electrode, a counter electrode separated by a reference electrode and a thin layer of electrolyte which monitor changes in the concentration of an analyte by voltammetric technology. Generally, electrochemical detection of estradiol employed chemically modified electrodes such as conducting polymers modified electrodes and nanoparticles, to increase detection efficacy [55,56]. Nevertheless, estradiol is weak in electro activity and easily passivates the electrode surface thanks to the special phenolic hydroxyl group in its structure. In addition, it needs high electric potential to be oxidized when detecting, but other materials present in the detecting system can be oxidized at the same time. So, interferences are observed and the effectiveness of estradiol detection is reduced in real sample analysis. All the factors add up challenges to develop estradiol electrochemical sensors with more stability, high sensitivity and specificity [39].

Electrochemical aptasensors in the tracing E2 are developed based on specific aptamer (Fig. 2A) that firstly designed in 2006 by Kim et al. [33]. In this work, Kim et al. immobilized a DNA aptamer via the avidin–biotin stringent interaction on Au electrode chip to evaluate the electrochemical signals generated from interactions between the target molecules and the aptamers. The square wave voltammetry and cyclic voltammetry values were measured to evaluate the chemical binding to aptamer. When 17β-estradiol interacted with the DNA aptamer, the current waned following the interference of bound E2 with the electron flow provided by a redox reaction between ferricyanide and ferrocyanide [33]. The DNA sensor exhibited a detection limit of 0.1 nM.

Dendrimers known as a class of 3D macromolecules with a well-defined and highly branched tree-like structure. The remarkable properties of dendrimers, say, controlled composition, biocompatibility, adequate functional groups, structural homogeneity and chemical fixation make them of suitable choices for emerging field of biosensing applications [57–59]. Along these advantages, spectroelectrochemical dynamics of Dendritic Poly (Propylene-Estradiol Biosensor, imine) – Polythiophene Star Copolymer Aptameric for 17β-estradiol detection was suggested by Olowu et al. They employed star copolymer G1PPT-co-PEDOT as a stand for immobilization of 76-mer aptamer to develop an electrochemical method for detection of 17β-estradiol. The aptasensor showed higher specificity for E2 compared to structurally similar compounds like naphthalene, estrone and 17α-ethylestradiol. The dynamic linear range of the sensor was 0.1–100 [60].

In a similar manner, Ke et al. studied a unique electrochemical aptasensor constructed on hierarchical dendritic gold modified boron-doped diamond electrode (BDD) (Fig. 3A). The obtained dendritic Au/BDD electrode has lower background current, higher capacity to immobilize biomolecules and better electrochemical performance. Estradiol aptamers were immobilized on the surface of the dendritic Au/BDD electrode through Au–S bond. Once estradiol enters the detecting system, it reacts with aptamers and significantly increases the interfacial electron transfer resistance, which leads to the increase of impedance signal and quantification of estradiol. The constructed estradiol aptasensor exhibits a wide linear range with the logarithm of concentration of E2 from 1.0×10^{-14} to 1.0×10^{-9} mol L^{-1} with a femtomolar level detection limit of 5.0×10^{-15} mol L^{-1}. High specificity is also evidenced by control experiments performed with the estradiol aptasensor in a co-existing system, including estriol, bisphenol A, diethyl phthalate, nonylphenol, resorcinol and atrazine [39].

In a study conducted in 2014, Huang et al. was produced a new electrochemical aptasensor for the determination of 17β-estradiol by immobilizing aptamers on the surface of gold nanoparticles and vanadium disulfide (VS2) nanoflowers modified GCE (Fig. 3B). Determination of 17β-estradiol and relationship between the peak current and the logarithm of 17β-estradiol concentration from 1.0×10^{-11} to 1.0×10^{-8} M with a detection limit of 1.0×10^{-12} M are applied with DPV. The aptamer sensor showed significant reproducible analytical performance and a high sensitivity, that could be successfully applied for the determination of 17β-estradiol in urine samples (recoveries 92.0–105.2%) [61]. Huang et al. worked on an electrochemical method based on the direct electron transfer (DET) of GOx for the detection of 17β-estradiol. They modified a glassy carbon electrode (GCE) with a composite made from copper sulfide (CuS) nanosheets, glucose oxidase (GOx) and AuNPs (Fig. 3C). The copper sulfide nanosheet acts as a relatively good electrical conductor. GOx as an indicator and AuNPs were dually modified on the electrode providing signal amplification for electrochemical sensing. To prepare this system, Single-step hydrothermal process was employed for preparation of CuS nanosheets. Subsequently, AuNP/GOx/AuNP complex were deposited on it for immobilization of E2-specific aptamer. After 17β-estradiol/aptamer hybridization on the electrode surface, the DET signal decreased as a result of the increasing spatial blocking around GOx molecules that results in the quantitative detection of E2. Using this platform, obtained detection limit and linear range with differential pulse voltammetry (DPV) were 6×10^{-14} M and 5×10^{-13} to 5×10^{-9} M, subsequently. After 1 week storing electrode in the refrigerator at 4°C, it retained 95.2% of its initial current response, represent good stability. The method exhibits good selectivity over

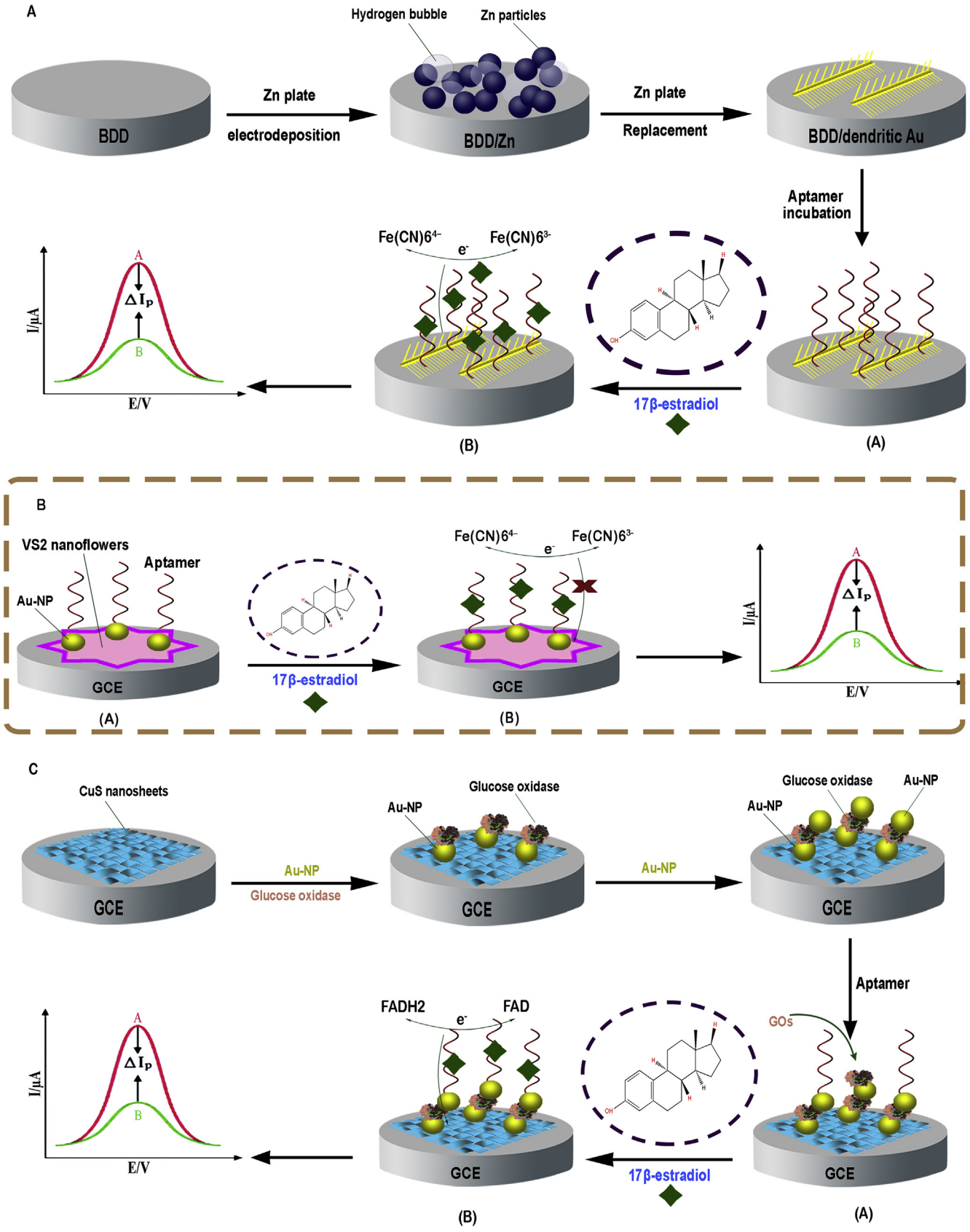


Fig. 3. Electrochemical-based aptasensors for E2 biosensing. The signal detection strategy based on (A) dendritic Au/BDD electrode [36], (B) AuNPs/VS2 nanoflowers/GCE [59], (C) CuS nanosheets/AuNP/GOx/AuNP [58].
Adapted from published papers [36,58,59].

1-aminoanthraquinone, bisphenol A and naphthalene even at 100-fold concentrations [62].

In another study, Zhu et al. used label-free electrochemical aptasensor for femtomolar detection of 17β-estradiol. Briefly, an electropolymerized copolymer bearing carboxylic acid groups, were coupled with amino-modified aptamer sequences, and then activated with EDC/NHS, before carrying out EIS measurements. They demonstrated an EIS aptasensor for E2 with wide dynamic range (1×10^{-15} to 1×10^{-6}) and femtomolar detection limit (1×10^{-15}), with considerable efficacy for detection in urine, and provided evidence of discrimination against potential interfering agents. They showed that this method can be successfully applied to other small molecule binding aptamers and validated a sub-standard design for high performance aptasensors that can quantify low molecular weight targets over an extremely wide concentration range in complex media [63].

In order to effectively overcome of labeling aptamers or adding additional probes into test system, Steen et al. chose a signal probe, the nickel hexacyanoferrate nanoparticles (NiHCF-NPs) and used in situ on the electrode because of its wonderful stability, good peak shape and easy synthesis. NiHCNFe nanoparticles are inorganic polymer analogs from prussian blue family [64]. NiHCNFe complexes have two different types, namely, NiHCNFe-II and NiHCNFe-III, which can be formed on the electrode alone or together by changing the preparation conditions [65]. The NiHCF-NPs as a signal probe was introduced in situ on the electrode by two-step deposition method to conversion the binding events between aptamer and estradiol into a measurable electrochemical signal, exhibiting well-defined peaks with good reproducibility and stability. When AuNPs were added on the NiHCF-NPs, provided a platform for immobilizing the aptamer and further increased the stability and conductivity of the signal probe. This fabrication showed a LOD of 0.8 pM with a LR of 1×10^{-12} to 6×10^{-10} M [38].

Carbon nanotube field effect transistor aptasensors (CNT FETs) has also been used for the determination of E2 in liquids. For instance, Zheng et al. demonstrated an increase in current over the range of 50 nM to 1.6 μM of E2 in real-time current response for the 35-mer E2 aptamer functionalized CNT FET, whereas, no response is observed in the same concentration of the E2 analyte with the 75-mer E2 aptamer. This was first example of electronic real-time detection of E2; pave the route for mobile sensors in quantitative and selective detection of E2 in liquids. The LOD of this method was reported to be 5×10^{-8} M with dynamic range from 5×10^{-8} to 1.6×10^{-6} M [66]. Huang and co-workers presented an Aptamer/AuNPs/cobalt sulfide (CoS) nanosheets aptasensor for the detection of E2 by employing guanine-rich complementary DNA sequence as signal amplification. In this assay, L-cysteine as sulfur donor was employed for synthesized 2-dimensional CoS nanosheet in a simple hydrothermal method. Then, a thiol group labeled 17β-estradiol aptamer assembled on CoS/AuNPs-modified electrode. The introduction of CoS nanosheets and AuNPs in the fabricated biosensor efficiently accelerated the electron transfer. When the aptamer captured E2, the binding of guanine rich DNA to the aptamer restrained. In absence of E2, a significant DPV signal appears because of methylene blue specific adsorption onto the guanine units of the detection probe. Dynamic ranges from 1.0×10^{-9} to 1.0×10^{-12} M and a detection limit of 7.0×10^{-13} M were reported [67].

Recently, a research group employed Size-controllable ultra-thin carboxylated polypyrrole nanotube transducer (A-UCPPyNTs) for extremely sensitive E2 FET-type aptasensors. The smaller diameter (40 nm) of UCPPyNTs generated a larger surface area and contributed to the biosensor enhanced performance, which increase the number of conjugated binding aptamers. Moreover, Present aptasensor demonstrate long-term storage stability (4 weeks of duration achieved in this work) and reusability. These properties resulted from the formation of covalent bonding in the fastening to a substrate electrode. Result showed this method was 10^3 times more sensitive (LOD ~ 1 fM) than the other reports [68]. A novel electrochemical sensor based on molecularly imprinted polymeric microspheres (MIPs) and multi-walled carbon nanotube/gold nanoparticle (MIP–MWCNT–AuNP) was developed by Futra et al. for detection of E2. MIPs are a stable material for sensing application because of high selectivity and sensitivity. The specific MIP microspheres to the E2, prepared via an easy photopolymerization technique. To accelerate electron transfer to the surface of the electrode, primarily the MWCNT grafted with AuNPs was deposited onto a carbon screen-printed electrode. Then specific MIP was coated onto the MWCNT–AuNP-modified SPE. When the E2 absorbed into the deposited MIPs, presence of E2 in samples could be detected and monitored by DPV. This sensor could detect E2 molecules from 1.0×10^{-15} to 1.0×10^{-6} M, with a LOD 2.5×10^{-16} M. The sensor represented a stability of 55 days with good reproducibility (RSD < 5%, $n = 5$) and regenerability (RSD < 4%, $n = 5$) [69].

2.3. Photoelectrochemical-based 17β-estradiol aptasensors

Although many efforts have been directed to detect estradiol by indirect electrochemical techniques, the concentration of estradiol is so low in the environment that the sensitivity is still not satisfactory. Therefore, it is difficult to achieve highly selective detection in complex environmental matrixes [40]. Coupling electrochemical detection with photoirradiation, the photoelectrochemical method has the advantages of both electrochemical and optical methods [70,71]. Especially, the PEC technique is an ultra-sensitive method as it uses different forms of detection (current) and energy for excitation (light), which has been applied to ultra-sensitive detection of various analytes [72]; But the PEC method lacks selectivity. How to achieve good selectivity in highly sensitive PEC detection of low levels of estradiol in the environment is still a challenging issue [40]. According to the instant demand to low levels of 17β-estradiol determination in the environment, an ultrasensitive PEC sensing platform based on anti-E2 aptamer, as the bio-recognition element, was developed onto CdSe nanoparticles-modified TiO2 nanotube arrays (Fig. 4). The designed PEC aptasensor exhibits excellent performance in characterizing estradiol with a wide linear range of 0.05–15 pM. The detection limit was lower than the previous reports (33 fM). The excellent sensing behavior toward estradiol can be attributed to the appropriate PEC sensing interface resulting from the excellent photoelectrical activity and preponderant tubular microstructure, the large packing density of aptamer on the sensing interface, as well as the high affinity of the aptamer to estradiol. The PEC aptasensor was successfully applied for detection of estradiol in environmental water samples without complex sample pretreatments, and the analytical results showed good alignment with those obtained by HPLC. Therefore, a simple and rapid PEC technique for determination of low levels of estradiol was established, having promising potential in monitoring environmental water pollution [40]. In another study, Du et al. established a highly sensitive turn-on PEC platform for E2 assay based on hematite/N-doped graphene/Au nanrods (AuNRs) hybrids as photoactive materials with SPR properties induced signal amplification. The fabricated aptasensor identified E2 in the range from 1×10^{-15} M to 1×10^{-9} M with a LOD 3.3×10^{-16} M. After 2 weeks storing aptasensor in 4°C, the aptasensor did not show a significant reduction in sensor performance, represent that the aptasensor had good stability [73].

3. Bioaffinity sensors for 17β-estradiol detection

A bioaffinity biosensor system is an analytical device composed relies on the specific binding of ligand to its cognate receptor,

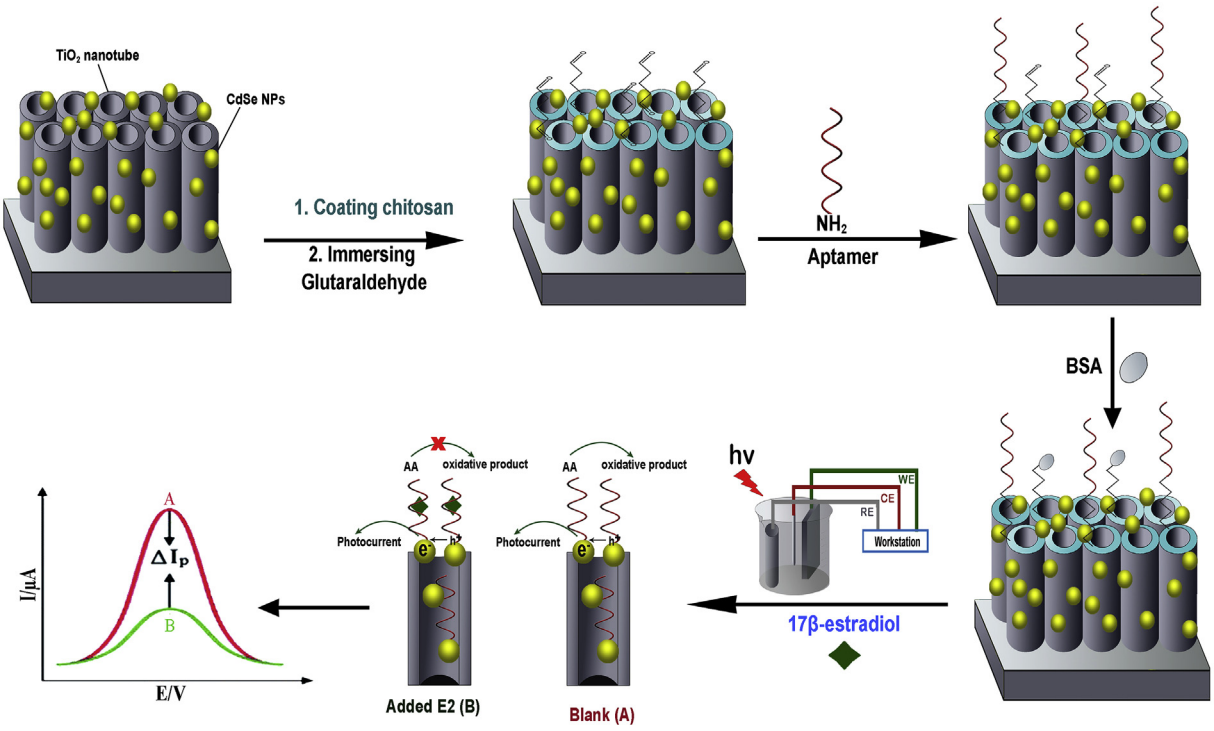


Fig. 4. Schematic illustration of the construction of E2 PEC aptasensor and the mechanism of PEC detection of 17β-estradiol. Adapted from published paper [37].

coated on a disk electrode. The bioaffinity sensor produces high sensitivity by using enzyme amplification methods. Function of the bioaffinity sensor is closely dependent on the turnover amount of the enzyme and the technique employed to sense the product of the catalyzed reaction [74]. In the past decade, several optical and electrochemical bioaffinity sensing methods have been established for monitoring of 17β-estradiol.

3.1. Optical-based 17β-estradiol bioaffinity sensors

Usami et al. have developed a simple assay method for the evaluation of estrogen receptor (ER) binding capacity of chemicals without the use of fluorescence-labeled compounds. In this study they used the solution competition assay by the BIACORE biosensor, a SPR biosensor, E2 as a ligand, human recombinant ERα (hrERα) as a high molecular weight interactant and test chemicals as analytes. The binding of test chemicals to hrERα was determined as a reduction in the hrERα binding to E2. The differentiation constant for the binding to hrERα was calculated for estrone (4.29×10^{-9} M), estradiol (4.04×10^{-10} M), estriol (8.35×10^{-10} M), by plotting the data according to an equation based on mass action law. The sensor chip stored in HBS for at least 2 months, sensor could be used over 1000 cycles without significant reduction in performance [75]. Similarly, Carman et al. developed a biosensor that detects estrogenic substances by means of a quartz crystal microbalance (QCM) with a genetically engineered construct of the hormone-binding domain of the ERα. The results revealed that this sensor responds to a variety of ligands that are known in binding to the ER, but No response was observed for non-binding substances such as progesterone and testosterone [76]. In this way, Wozei and colleagues report bioaffinity platform for detection of estrogen in water samples. In this study estrogen-sensitive yeast strain RMY/ER-ERE are exposed to the E2 in a water sample, the uptake of the E2 and the subsequent production of β-galactosidase enzyme occurs rapidly, with maximum enzyme-catalyzed product formation evident after 30 min of exposure. They use fluorescein di-β-d galactopyranoside as a β-galactosidase substrate to give a fluorescent product (fluorescein) which can be detected by fluorescence microscopy [77]. De et al. developed FRET-based biosensors that permit the direct in vitro evaluation of ER ligands. The system includes ER ligand-binding domain (LBD) flanked by the FRET donor fluorophore, acceptor fluorophore, yellow fluorescent protein (YFP) and the cyan fluorescent protein (CFP). For enhance in the magnitude of the FRET signals in response to ligand-binding, Alanine 430 has been changed to Aspartate. This modification increases the FRET signal by more than fourfold compared to the wild-type LBD. 7×10^{-8} M as lower concentrations are below the sensitivity limit of the assay [78].

3.2. Electrochemical-based 17β-estradiol bioaffinity sensors

Murata et al. developed a bioaffinity sensor aiming at the detection of estrogen. The ligand-binding domain of DNA sequence encoding human estrogen receptor was expressed in bacteria with N-terminal histidine-tag. The protein was purified by affinity chromatography, which is based on a specific interaction between the Ni(II) chelate adsorbent, and histidine-tag. They used thiol-modified iminodiacetic acid and histidine tag to immobilized protein on an Au-electrode with Ni (II)-mediated chemisorption. The reversible electrochemical reaction of a $[Fe(CN)6]^{4-}/[Fe(CN)6]^{3-}$ redox couple was suppressed by the attendance of estrogen in a concentration-dependent manner showed by cyclic voltammetry (CV). In this case, detection limit was 0.8×10^{-12} M and the linear range was obtained 1×10^{-12} to 6×10^{-10} M [79]. In another study, Xia et al. employed a nanostructure electrochemical biosensor to directly detect and screen estrogenic substances based on ER binding without the use of radio or enzyme-labeled compounds. They immobilized ERs in supported bilayer lipid membrane (s-BLM) modified by AuNP and the properties of the modified electrodes were characterized by impedance spectroscopy and cyclic voltammetry. The results indicated that the biosensor was able to

detect the E2 with an acceptable linear correlation ranging 5–150 ng L^{-1} and a detection limit of 1 ng L^{-1}. The biosensor showed good repeatability and reliability, and the AuNP greatly increases the stability and sensitivity of the biosensor [80].

4. Conclusion and future perspectives

Endocrine disrupting chemicals (EDCs), especially 17β-estradiol (E2) are one of the main environmental contaminants, as they seriously interfere with the normal endocrine function of human and wildlife. In this review, aptasensors and bioaffinity sensors for 17β-estradiol detection, including both optical and electrochemical technologies have been discussed. After a description of bio-sensing assays for 17β-estradiol, we founded the most researches focus on the presence of estrogens in environmental water because they are considered to be the rich sources of estrogens; but no studies have been devoted to the determination of estrogens in milk matrices. While, the content of 17β-estradiol in commercial milk shows a sustained rise [81,82]. Therefore, it is of significance to use modified bio-sensing assays in the analysis of 17β-estradiol in milk samples. The present state of the art of nanomaterials-based aptasensors for 17β-estradiol detection showed some limitation. The major challenge in respect to these methods is the most of long-sequence aptamers showed poor performance in detection sensitivity such as 17β-estradiol 76-mer. Besides, the long aptamers bind more tightly than short aptamers as they have more bases bound to the surface of nanoparticles [37]. To overcome these obstacles, we would be improved by achieving better mechanism of DNA adsorption onto the surface of AuNPs and the development of a new aptamer design strategy. Accordingly, in 2015, Akki et al. introduces the new E2 aptamer with dissociation constants (K_d values) of 0.6 μM which is 74-fold more sensitive for E2 than a formerly reported aptamer [83]. By accomplish this modification; it seems that some of these fabrications will have potential to be marketed in the near future.

Considering the broad application of nanomaterials, integration of modified nano-biosensing technologies and microchip devices (microfluidic systems) are suggested as possible future prospects for the ultra-sensitive and simultaneous determination of steroids and their metabolites in various samples. The microfluidic-based systems and lab-on-a-chip (LOC) devices offer significant advantages, including high throughput, speed, portability, cost, and automation for various usages [41,84,85]. Microfluidics-based devices are on-chip sensing devices, coupled with different functional units and combined into a miniaturized analytical system [86], require only a small volume of fluid (~10 μL) [87]. Therefore, microfluidic devices significantly reduce the consumption of samples and reagents, the complexity of operation processes, and the length of assay time without compromising specificity and sensitivity [88]. It is expected that the technique will be highly useful in the simultaneous determination of steroids and their metabolites in the near future.

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