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An electrochemical strategy for tetracycline detection coupled triple helix aptamer probe with catalyzed hairpin assembly signal amplification

Yonghong Wang[a], Liu Yao[a], Ge Ning[b], Yaohui Wu[a], Shun Wu[a], Shaoming Mao[a], Gao-Qiang Liu[a,*]

[a] Hunan Provincial Key Laboratory for Forestry Biotechnology & International Cooperation Base of Science and Technology Innovation on Forest Resource Biotechnology, Central South University of Forestry and Technology, 410004, Changsha, China
[b] International Education Institute, Hunan University of Chinese Medicine, 410208, Changsha, China

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ABSTRACT

Incorporating elements of triple-helix aptamer probes (TAP), catalyzed hairpin assembly (CHA) signal amplification and host-guest recognition, a novel "signal-on" sensing strategy for sensitive electrochemical quantification of tetracycline (TC) was reported unprecedentedly. TAP was formed involving an aptamer loop, two-segment stems and a triplex oligonucleotide serving as trigger probe. Then, the trigger probe would be released from TAP once the target presented due to the conformational variation of TAP induced by aptamer binding event, sparking off the upcoming CHA amplification reaction, in which two coexisting DNA hairpins (H1 and H2 both modified with the electroactive molecules) would hybridize into plentiful H1–H2 double helices. Afterwards, the Exonuclease III was added, demolishing double helices and simultaneously releasing plentiful electroactive molecules which were capable of diffusing onto the electrode surface under the assistance of β-cyclodextrin due to host-guest recognition, where appreciable signals were enriched and generated. As thus, considerably slight amounts of targets though, emitted trigger probes, yet efficiently engining spectacular CHA cycles of reactions through which amplified signals were yielded, and in turn progressively enabling the sensitive target detection done. Under optimal conditions, the growing signal stayed a linear relation along with the logarithm of the target concentrations ranging from 0.2 nM to 100 nM, the detection limit reaching as low as 0.13 nM. This approach was desirable regarding to sensitivity, detection limit and range, prospectively rendering a service for diverse targets detection by easily replacing the matched aptamer loop of TAP.

1. Introduction

Possessing merits of broad spectrum antimicrobial property, robust stability and moderate price, tetracycline (TC), one of the most classic representatives in antibiotics, was substantially exploited in diseases prevention and treatment and alternatively as feed additives in breeding animals (Wang et al., 2014; Sassman and Lee, 2005). In a long run, the TC abuse resulted in the accumulation and residue in meats, eggs, milk produced by these animals, posing an overwhelming threat to the health of their consumers. Excessively exposed to TC, humans were vulnerable manifested in organic damage covering stomach, intestines, liver etc. Particularly, children were extremely allergic to TC with even limited amount of which they would be interfered in with the calcium absorption and likely to develop dental and skeleton disorders. Besides, under the TC contamination, the super bacteria were survived due to gene mutation, accordingly compromising the treatment efficacy of bacterial infection (Yang et al., 2018a; Wenk et al., 1981). Being apprehensive about its evil side, administrations formulated a relatively strict standard for TC residue. For instance, European Union stipulated a detailed and maximized limits towards TC residues as 0.1 mg/kg for milk, 0.3 mg/kg for liver and 0.01 mg/kg for honey respectively (Kelnerova et al., 2014). Therefore, a cogent analytical strategy with excellent preciseness, specificity and efficiency is imperatively vital to stuff the huge needing gap of TC assessment in fields of clinical medicine, food safety and environmental conservation.

Diverse analytical approaches hitherto were adopted for TC assay (Huang et al., 2018), such as high-performance liquid chromatography (Gissawong et al., 2019), thin-layer chromatography (Naidong et al., 2003), capillary electrophoresis (Moreno-Gonzalez et al., 2018), enzyme-linked immunosorbent assay (Wang et al., 2019), colorimetric assay (Wang et al., 2016; Chen et al., 2017; Zhou et al., 2018), fluorescence assay (Yan et al., 2019), surface plasmon resonance (Wang et al., 2018), chemiluminescence (Zeng et al., 2017), surface enhanced Raman scattering (Pinheiro et al., 2019), electrochemical assay (Rad

* Corresponding author.
E-mail addresses: bionano@163.com (Y. Wang), gaoliuedu@csuft.edu.cn (G.-Q. Liu).

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and Azadbakht, 2019; Li et al., 2019), electrochemiluminescence (Guo et al., 2011; Gu et al., 2013) and photoelectrochemical (Sui et al., 2018). Despite these methods as proposed made indelible progress after much effort being invested, but somehow they were implicated by inherent dissatisfiers of insensitivity, unaffordable equipment, tedious and intricated process and requiring sophisticated operators. Electrochemical sensors, instead, came into the view as a compelling option for biosensing and captured abundant imagination bolstered by desirable sensitivity, specificity, inexpensiveness, miniaturization of instruments, and acceptable operability. Signal amplification assisting in the ultrasensitivity of analytic performance was of significant consequence. Catalytic hairpin assembly (CHA) performed a reaction process of kinetics controlling, during which a successive chain of hybridization was consecutively undergone between two types of metastable DNA hairpin probes with no enzymes required, exhibiting an ideal predictability and precise controllability. It was exactly thanks to the features of enzyme-free and non-energy-actuated isothermal process to make increasingly its way being a powerful DNA molecular engineering tactic which was adjusted to a series of analytic protocols as a robust amplifying element (Yin et al., 2008; Qing et al., 2019). Therefore, the coordination of electrochemical methods and CHA amplification were conceivable to become a competitive candidate among sensors.

Characterized with unique structure, relying on the mechanism of Watson-Crick and Hoogsteen base pairings, triple-helix aptamer probe (TAP), a new scientific favorite, was emerging and engaged in the construction of biosensors, consisting of an aptamer sequence as the loop with two segments arms flanked by sides and a triplex oligonucleotide. It enjoyed salience arisen probably from reasons that to begin with, it was identically structurally stable as duplex DNA, and then, it covered a longer aptamer sequence, where superior selectivity or even higher sensitivity were boosted (Zheng et al., 2011; Tang et al., 2017), Lastly, it conserved operational simplicity and economic efficiency owing to replaceability of the aptamer with needlessness of probes redesign for the signal transduction, facilitating its broad adaptability in analyzing assorted targets. Given these virtues, TAP got accumulatively eye-catching and came into service as a key concept for target recognition and signal transduction introduced into certain numbers of biosensing platform designs (Bagheri et al., 2018).

Due to its individuality of exclusively catalyzing activity in removal of mononucleotides from the blunt or the recessed 3′-hydroxyl termini of double-stranded but scarcely being efficient in single-stranded DNA, Exo III was frequently assigned to be a key component for construction of ranges of sensors (Liu et al., 2016; Zhang et al., 2018). Besides, it was a special enzyme independent from sequence requiring no given recognition sites, consecrating service in establishment of diverse platforms coupled with approaches of fluorescence, colorimetry, electrochemistry, chemiluminescence for the assessment of a variety of targets.

Considering aforementioned aspects, namely in combination of virtues of TAP identification mechanism, CHA signal amplification, Exo III-assisted signal release and host-guest recognition,a TC electrochemical biosensing strategy was thereby proposed. Firstly, the unique structured TAP was devised of which a target specific aptamer served as the loop, two DNA segments flanked as the stems, and a DNA trigger matched simultaneously with the two stems. The recognition and binding events were done upon the addition of target by the aptamer, furthering the transformation of the TAP and thereat the departure of the DNA trigger. Then the released trigger would initiate the CHA reaction, during which two Fc-modified DNA hairpins (H1 and H2) would hybridize into H1–H2 double helices. Sequentially, the Exo III participated, cleaving the helices and accordingly releasing the Fc signal indicators which would diffuse onto the electrode surface through the shortcut provided by the β-cyclodextrin due to host-guest recognition, whereupon detectable DPV signals would respond consequently. This principle was commendable since it needed only a small quantity of targets to fuel magnificent CHA cycles, during which rounds of amplified signals would be produced and captured exactly corresponding proportionally to the targets quantity in return, providing a more sensitive measurement for the targets. In this way, a highly sensitive and specific electrochemical approach was presented which to the best of our knowledge was unprecedentedly reported concordantly assembling these whole novel factors, implying its promising prospective for application in evaluation of assorted targets after a simple replacement of the corresponding aptamer.

2. Experimental section

2.1. Reagents and materials

Tetracycline, chloramphenicol, kanamycin, chlortetracycline, norfloxacin and oxytetracycline were all bought from Aladdin (Shanghai, China). While mercapto-β-cyclodextrin (β-CD-SH) was bought from Sigma-Aldrich (Sigma-Aldrich, China) and used with no treatments. Exo III (the concentration of 200 U/μL) dissolved in 50 mM Tris-HCl containing 5 mM $MgCl_2$ was purchased from Takara Biotechnology Co. Ltd (Dalian, China). The other participated reagents were all in analytical level employed untreated as purchased. Diluted from the Millipore Milli-Q system (Millipore, Billerica, MA, 18.2 MΩ cm), the ultrapure water, as the solvent was utilized to do the preparation for solutions. The DNA sequences were all customized (synthesis and purification) by Shanghai Sangon Biotechnology Co. Ltd. (Shanghai, China). Playing the role of realizing the signal transmission, Ferrocene (Fc) was modified on 5' end of H1 and H2 respectively. The oligonucleotide sequences were elucidated in Table S1 (supporting information).

2.2. Pretreatment of electrode

Including a gold working electrode, an Ag reference electrode, and a gold counter electrode, the portable screen-printed electrode (SPE, DRP-C220AT, Metrohm China Limited) was adopted. Foremost, in an ultrasonicator, the electrodes were cleaned with ethanol for 10 min and then experienced the treatment by pure water for around 10 min for removal of the remanent organic contaminants. Subsequentially, the electrodes were rinsed with a great deal of pure water. It was all with CHI660E electrochemical workstation (Shanghai Chenhua Instrument Corporation, China) to carry out each electrochemical step at room temperature. Also, it was at room temperature to operate DPV in sensor interrogation. The potentials referred to the Ag reference electrode. By independent experiments, each step was repeatedly operated for no less than five times.

2.3. CHA reaction

Prior to usage, we heated every oligonucleotide at 90 °C for 5 min, and cooled them down to room temperature for following experiments. The hybridization occurred between the aptamer and trigger probe was in 200 μL 10 mM pH 6.2 Tris-HCl containing 100 mM NaCl, 5 mM $MgCl_2$ and 5 mM KCl. After process illustrated above, a succession of TC concentrations were added dropwise into the solution and afterwards incubated for 60 min. The CHA reaction was undergone in 10 mM Tris-HCl containing 100 mM NaCl and 5 mM KCl. For the insurance of sound occurrence of CHA reaction, the mixture, including 200 nM H1, 200 nM H2 and the above mentioned reaction solution containing a range of concentrations of target was incubated at 37 °C for 90 min. After that, 2 μL Exo III (10 U/μL) was adjusted to the mixture solution at 37 °C for sufficient reaction.

2.4. Determination of TC

At room temperature, at the first place, 5.0 μg/mL β-CD-SH was dropped onto the surface of the electrode and then incubated for 2 h. Then, by means of rinsing with PBS buffer for 3 times, the remained β-CD-SH was removed from the electrode surface. Lastly, this Exo III

treated reaction solution was pinpointed to assay targets with various concentrations in optimal condition using β-CD/SPE. 10 μL reaction solutions were dropped onto the β-CD/SPE's surface. After capturing for 1 h, the electrode was rinsed with PBS buffer prior to electrochemical measurements.

2.5. Selectivity

The specificity of the as-proposed strategy was evaluated by adding analogs into the sensing platform. As representatives, five interfering analogues-chloramphenicol, chlortetracycline, kanamycin, norfloxacin and oxytetracycline at the concentration of 10 nM were nominated for testing the specificity of the strategy, undergoing the equal experimental procedure as the one did for TC. Then, the results were in comparison with the one adding 1.0 nM TC.

2.6. Determination of TC in real samples

The milk powder obtained from supermarket was selected as the real sample for the evaluation of the reliability of this assay. At first, the sample (1.0 g) was added into a 10 mL centrifuge tube and diluted with 5 mL ultrapure water. Next, 1 mL 10% trichloroacetic acid and 1 mL chloroform were added and vortex-mixed for 5 min for proteins precipitation and dissolution of other organic matters in the matrix. Afterwards, the mixture was ultrasonically treated for 30 min and then centrifugation with the speed of 10,000 rpm for 5 min was performed for separation of the deposit. While the supernatant, for further obtaining the final supernatant at analytical level, was transferred into another centrifuge tube and centrifuged at 10,000 rpm for 10 min for removal of the deposit once again. Thus, the recovery was assessed in final supernatant adopting TC at different concentrations. The reliability was established referring on evaluating the recovery rate in final supernatant samples. At standard samples, the samples were spiked with different concentrations of TC. The process was the same with the one elaborated above.

3. Results and discussions

3.1. Sensing principle for TC detection

In Fig. 1, the principle of this tactic was elucidated: In the absence of the target, the trigger in the TAP remained rigid subjected to the Watson-Crick and Hoogsteen base paring, hybridizing with the stems flanked. While the detection was on as long as the targets were introduced by initially altering the TAP conformation owing to the robust affinity of the aptamer bound with the target as the spatial matching, electrostatic and hydrogen bond effects, liberating the trigger. Then this trigger ignited a CHA reaction, where two coexisted Fc-DNA hairpins would hybridize into double helices. Afterwards, the Exo III, a cleaver hydrolyzing exclusively the double helices, was added to destroy the hybridization and meanwhile liberate the signal molecules-Fc. Lastly, the Fc diffused onto the electrode surface through the speedy pattern facilitated by the β-cyclodextrin via host-guest recognition, where an enriched and detectable signals were yielded. Therefore strong DPV signals proportional to the TC concentration could be determined in accordance with this principle.

Notably, some designing knacks were considered to have upgraded the performance of this tactic: (I) it adopted TAP, an illustrious contributor to the specificity and sensitivity thanks to the robust recognition element-constitution of aptamer loop. Also, the portion of DNA trigger played the role of bridge connecting the two key phases-target recognition and signal transduction. (II) As for the CHA section, the extended 3′- terminus of H1 and H2 was devised whose hairpin structure with 3′ protruding termini could prevent H1 and H2 from the cleavage of Exo III before the DNA trigger was involved (Fig. S1). But when the CHA reaction started, rounds of hybridization between two hairpins occurred automatically, resulting in fold increase of signal indicators modified with the hairpins ready for being released, thereby effectively promoting the sensitivity of the assay. (III) The employment of β-cyclodextrin fulfilled the enrichment of the signals bolstered by host-guest recognition in the period of signal molecule capture, doing its bit for the sensitivity improvement. By right of above behalves, a sound electrochemical aptamer sensor was fabricated for the assay of TC.

3.2. Feasibility of the sensing strategy

The feasibility for sensitive electrochemical assay of TC employing the CHA signal amplification and Exo III-assisted signal release was investigated. In Fig. 2, DPV signal responses before and after the addition of the targets were shown. As displayed by curve a, there revealed scarcely any of the DPV readouts when β-CD-SH was modified on the surface of the electrode, suggesting that β-CD-SH did not generate signals by itself and nor would it influence the upcoming experiments. Curve b and curve c were the signal of Fc-H1-DNA and Fc-H2-DNA respectively captured by the β-CD modified electrode. Alike, prior to the presence of the target, a comparatively negligible DPV background signal (curve d) was exhibited on account of TAP structure conservation with the DNA trigger unreleased, which hindered the onset of the CHA reaction. Accordingly, the signal indicators-Fc, modified on the H1 and H2, were impeded to diffuse to the electrode surface due to the steric hindrance between the dsDNA and electrode. Instead, when TC was introduced, the signal response enhanced steeply (curve e) because the target estranged the DNA trigger away from the TAP which was drawn into CHA reaction. After that, the hybridized H1–H2 complexes were digested by the Exo III simultaneously with the Fc liberated, which was captured accurately by the β-CD-SH and transformed into obvious DPV readouts. Hence feasibility of the method was validated substantially.

3.3. Optimization of experimental parameters

In order to display a superior electrochemical sensing performance in detection, parameters that was deemed to be significantly impacting on the experiments were respectively optimized including the concentration of Exo III, variables TAP concentration, CHA reaction time, capturing time between Fc and immobilized β-CD. At first, the concentration of Exo III was assessed through observing the DPV readouts. When the concentration of Exo III increased, the peak current of oxidation enhanced at the mean time. However, when the Exo III concentration exceeded 20 U, the rise of peak current was no longer obvious, demonstrating that the plateau of concentration was almost arrived at for the cleavage reaction (Fig. 3A). Therefore, the Exo III concentration was selected at 20 U as the optimal one for the subsequent experiment.

For the better performance of the electrochemical signal, the concentration of TAP was measured in 0.1 M PBS. After the addition of various TAP concentrations into the solution, in Fig. 3B, the currents of modified electrode were demonstrated, revealing that the current upgraded along with the increase of TAP concentration. However, when TAP concentration reached 3 μM, the current started to level off, manifesting that the TAP concentration was saturation-approached. As a result, TAP concentration at 3 μM was fixed as the optimal value.

The time covering the CHA reaction affected severely the sensitivity of the proposed method, which thus was investigated also. As one could see in Fig. 3C, the current got stronger with the expansion of reaction time ranging from 10 to 60 min. Nevertheless, as the homogeneous reaction time was more than 90 min, the current value kept steady, manifesting that the completion of homogeneous reaction could be realized when 90 min was chosen as the optimal reaction time for the assay.

The capture time between Fc and β-CD, as another identically

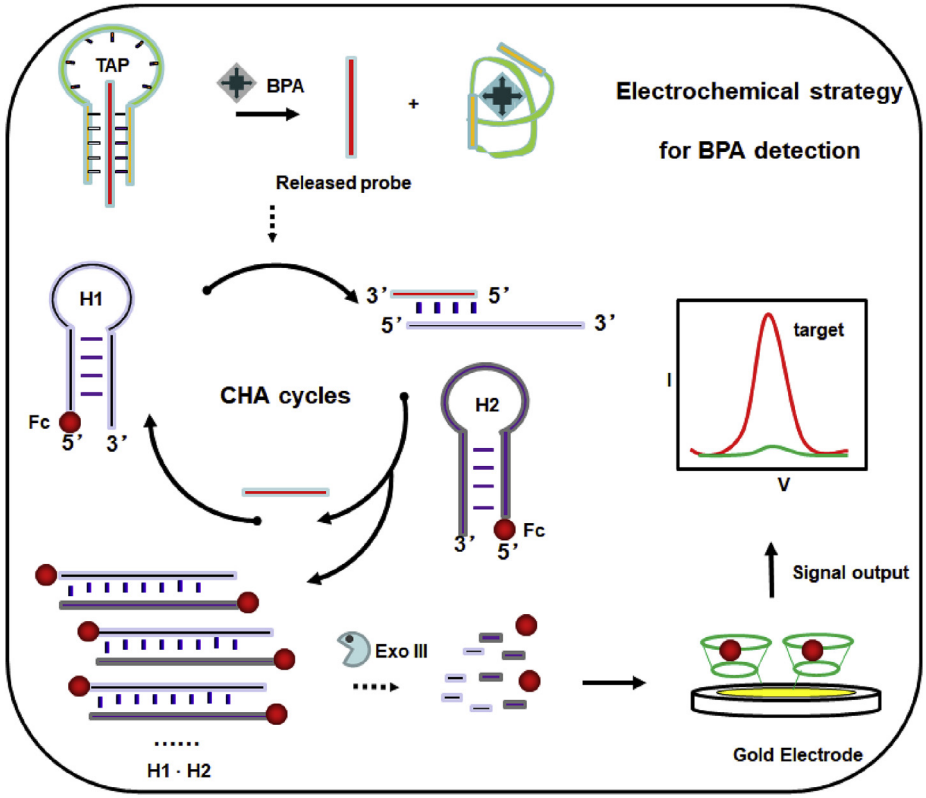

Fig. 1. Sensing principle of electrochemical strategy for TC detection based on triple helix aptamer probe and catalyzed hairpin assembly signal amplification.

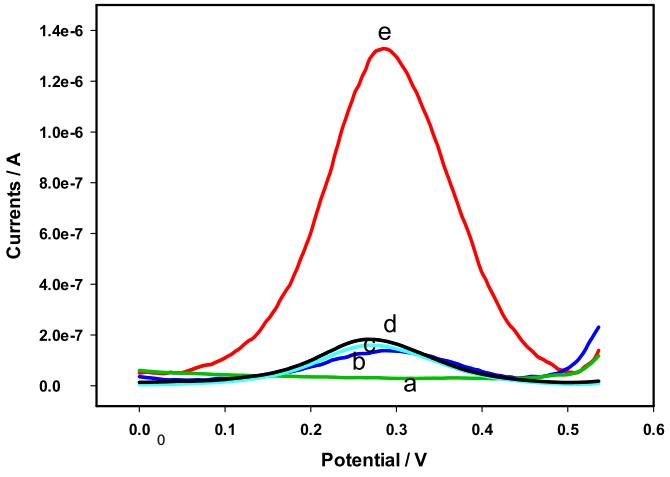

Fig. 2. DPV curves of β-CD modified SPE (curve a), 200 nM H1 (curve b), 200 nM H2 (curve c), in the absence of TC (curve d) and the in the presence of TC (curve e), respectively, and the electrodes were investigated in 0.1 M PBS +0.1M KNO_3.

crucial factor, was tested in view of the close relationship between the sensitivity and the capture efficiency. Here the capture time was optimized for the ensurance of the maximized amount of signal molecules arriving at the electrode surface. The current signal increased, as displayed in Fig. 3D, when capture time passed from 10 min to 120 min. However, when the time was over 60 min, the signal became steady with no apparent increase observed, indicating the saturation of capture. Therefore, 60 min was pinpointed to be the capture time optimized.

3.4. Analytical performance of the biosensor

With the experimental conditions optimized, integrating the merits of TAP, the CHA signal amplification and host-guest recognition of β-cyclodextrin, the electrochemical biosensor was successfully fabricated for the efficient assay of TC. Upon the participation of TC, as exhibited in Fig. 4A, the responses of currents raised correspondingly with the increase of the concentrations of TC. Furthermore, as shown in Fig. 4B, the peak current changes of the system maintained a linear dependence with the logarithm of the target concentrations in a range of 0.2 nM–100 nM. The equation was I (1e-6A) = 8e-7 log C_{TC} + 9e-7 (R^2 = 0.9713). In the low concentration range, the peak current changes maintained a linear dependence with the TC concentration of 0.2 nM–1.0 nM. The equation was I (1e-6A) = 9e-8 C_{TC} + 1e-7 (R^2 = 0.9942), LOD was derived to be 0.13 nM in accordance with the formula $I_{LOD} = I_0 + 3\,S_0$, in which I denoted the peak current value in the presence of TC and S_0 was the standard deviation of background signal. The superior performance of this assay was attributed to the TAP design, in which the precise biorecognition of aptamer could be linked with the liberation of trigger probe used for CHA signal amplification, collectively enabling the sensitivity improvement of the method. Besides, the other dedicator went to Exo III-assisted signal release and exact signal capture via the host-guest recognition of β-cyclodextrin, making it possible for the signal indicator to be enriched and yielded, and thus heightening the sensitivity to some extent. Admittedly, the as-developed approach, in consideration of the LOD, performed better than that of newly reported or/and traditional equipment-used methods (Table 1).

3.5. Selectivity test

Five TC analogs were selected for the evaluation of the specificity of this method and their influence on the currents intensity was tested through observing the variations before and after their addition. The

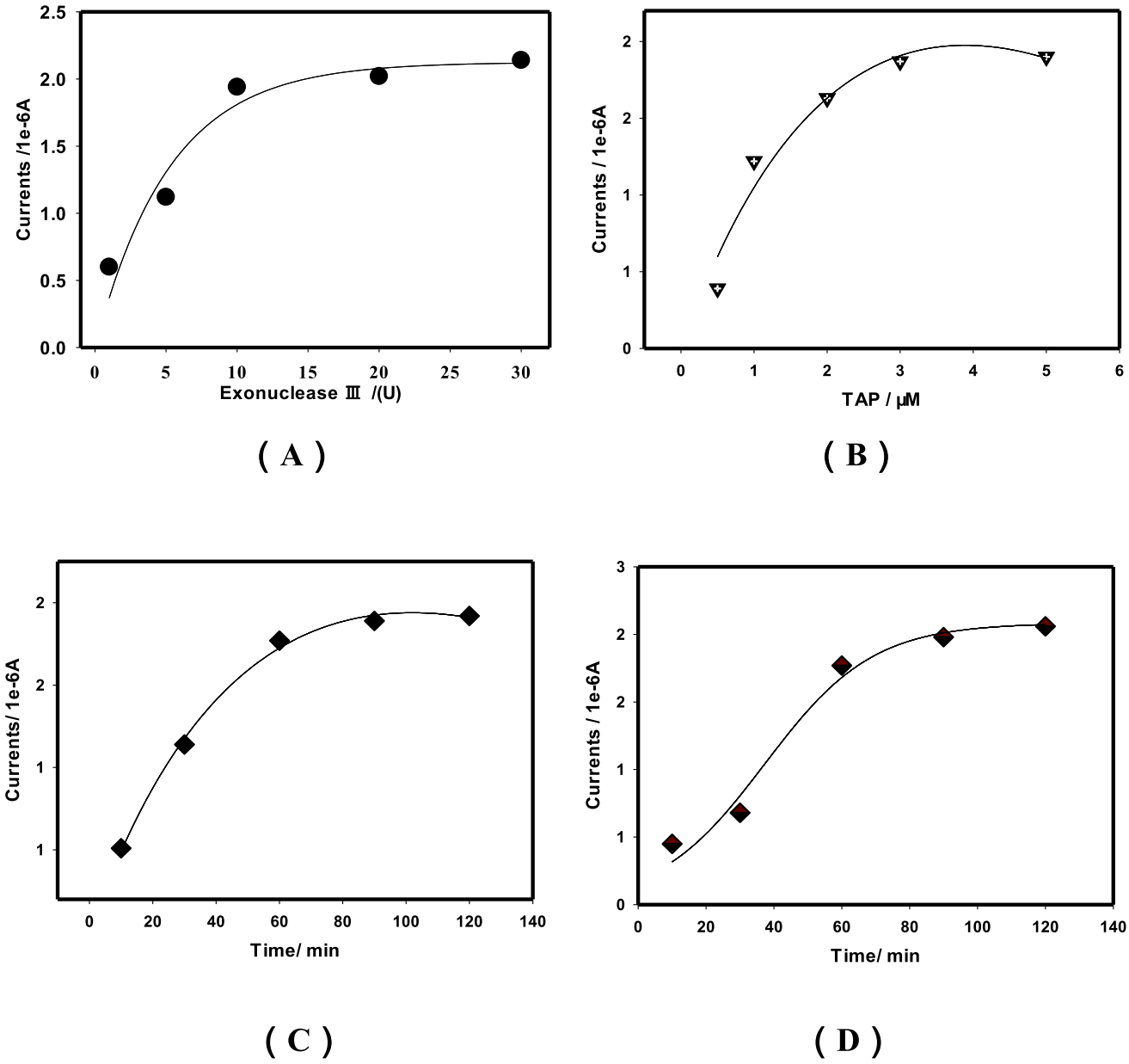

Fig. 3. Significantly impacting on the experiments factors on the currents intensity of detection system. (A) Exo III concentrations, (B) TAP concentrations (C) the time of the CHA reaction and (D) capture time between β-CD and signal molecules.

assays of analogs were carried out at the concentration of 10 nM whereas the TC was fixed at the concentration of 1.0 nM. The target, as displayed in Fig. 5, was the only one that could result in an evident signal enhancement sensed by the system. As a contrast, there remained barely any intensity changes in the currents when the analogs presented alone or as a whole, which manifested that TC could be differentiated by the fabricated sensor readily when other TC analogs interfered in, showing a satisfactory selectivity for target. Besides, the stability of the modified electrode was evaluated by storing the modified electrode at 4 °C and measuring the values of current at different times (1 day, 3 days, and 7 days) under the same conditions (Fig. S2). The values of current had no obvious difference and the relative standard deviations were 5.9%, 6.8% and 6.2% respectively, suggesting that the proposed assay had a satisfying stability for TC detection.

3.6. Biosensing in actual samples

A milk sample solution was used to investigate the analytical reliability of the approach. In the phase of sample pretreatment, organic substances as protein and fat were removed. Prior to the addition of TC into the solution, using the constructed assay, no TC was detected exceeding the LOD of the method in the milk sample. Afterward, TC at various concentration were added into the solution for the performance of recovery experiments. The samples were spiked with target at many levels before the recovery ranged from 92.8% to 107.7% with RSD (n = 5) lower than 7.2%, demonstrating a good result. Hence the established electrochemical biosensors was qualified being a powerful candidate in real samples with satisfactory accuracy in target determination.

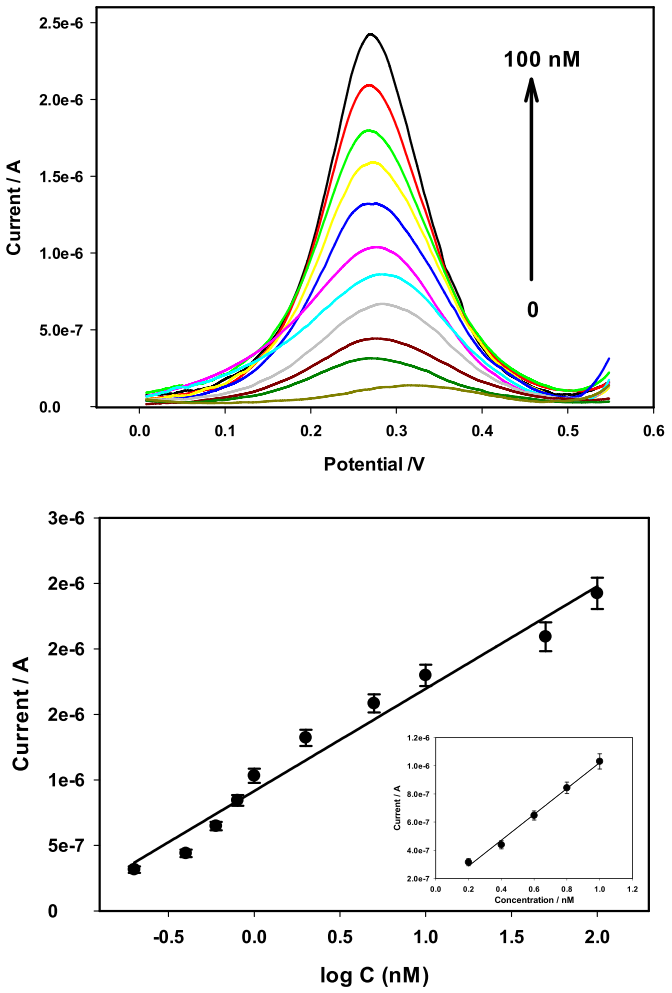

Fig. 4. A) DPV of developed system in the presence of different concentrations of TC (0.2, 0.4, 0.6, 0.8, 1.0, 2.0, 5.0, 10.0, 50.0, 100.0 nM) in 0.1 M PBS buffer; B) Linear relationship between currents and target concentrations.

4. Conclusions

An assay with ideal sensitivity and selectivity, to sum up, for TC quantification was accomplished aggregating the TAP construction through accurately recognizing the target to dissociate the trigger probe, CHA system via introducing the small amount of triggers to produce multiple signals obtaining signal amplification, and the β-cyclodextrin for the fulfillment of signal enrichment via the host-guest interaction. This assay of TC revealed a broad detection range, low detection limit, acceptable accuracy as well as simultaneously requiring neither a complicated preparation nor a large quantity of samples. It was, in comparison with the previous-proposed methods, remarkably efficient, sensitive, easy-operated, bearing a profound potential to be

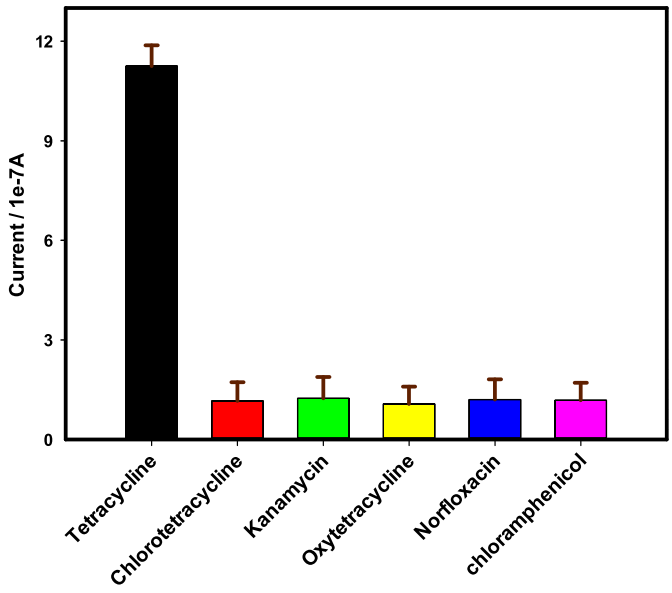

Fig. 5. Specificity of the electrochemical strategy. Five interfering analogues including chloramphenicol, chlortetracycline, kanamycin, norfloxacin and oxytetracycline. The concentrations of analogues and TC were 10 nM and 1.0 nM respectively.

miniaturization and integration for TC detection. Moreover, in a broader sense, it implied a tremendous applying value to be popularized in evaluating the rest of targets owing to the flexible replaceability of the corresponding aptamer in TAP, thus opening up a diversified platform for ranges of targets evaluation in real aqueous biological samples with superior detecting performance.

CRediT authorship contribution statement

Yonghong Wang: Methodology, Conceptualization, Writing - original draft, Formal analysis. **Liu Yao:** Methodology, Data curation, Validation. **Ge Ning:** Formal analysis, Writing - review & editing. **Yaohui Wu:** Software, Formal analysis. **Shun Wu:** Investigation, Formal analysis. **Shaoming Mao:** Project administration, Supervision, Writing - review & editing. **Gao-Qiang Liu:** Resources, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1
Comparison of different assays for TC sensing.

Sensing element	Technique	Analysis time(min)	LOD (μM)	Linear range (μM)	Ref
Triple-helix molecular switch	Colorimetric	95	2.66×10^{-4}	0.0005–0.01	Ramezani et al. (2015)
Gold nanoparticles	Colorimetric	40	0.38	0.95–29.25	Shen et al. (2014)
M-shape aptamer	Electrochemical	125	4.5×10^{-4}	1.5×10^{-3}-3.5	Taghdisi et al. (2016)
Reduced graphene oxide/Fe_3O_4 nanoparticles	Electrochemical	270	6.0×10^{-4}	1–5000	Zhan et al. (2015)
Aptamer	Electrochemical	1485	2.5×10^{-4}	1.25×10^{-3}-11.25	Chen et al. (2014a)
Carbon quantum dots	Fluorescent	15	0.05	25–15000	Hou et al. (2013)
Xylan-derived carbon quantum dots	Fluorescent	40	6.49×10^{-3}	0.05–20	Yang et al. (2018b)
$Ru(bpy)_3^{2+}$-doped silica nanoparticles	ECL	–	0.23	1–100	Chen et al. (2014b)
CHA and TAP	Electrochemical	210	1.3×10^{-4}	2.0×10^{-4}- 0.1	This work

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bios.2019.111613.

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