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Impedimetric detection of Fumonisin B1 and its biointeraction with fsDNA

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ABSTRACT

The electrochemical interaction of mycotoxin, Fumonisin B1 (FB_1) with fish sperm double stranded DNA (fsDNA) was investigated by using electrochemical impedance spectroscopy (EIS) technique. The pencil graphite electrodes were used for impedimetric detection of fsDNA and FB_1, and also the impedimetric monitoring of surface confined interaction of FB_1 with fsDNA under the optimized conditions. The experimental conditions; the concentration of DNA and FB_1 and the interaction time of FB_1 with fsDNA were firstly optimized. The main features of impedimetric DNA biosensor, such as its detection limit with the reproducubility were also discussed. The selectivity of detection of interaction between FB_1 and fsDNA was also explored in the mixture samples containing FB_1 and each of other mycotoxins, such as zearalenone (ZEN), deoxyvinalenol (DON) in order to examine the selectivity of impedimetric DNA biosensor.

1. Introduction

Mycotoxins such as Fumonisin B1 (FB_1), deoxynivalenol (DON) and zearalenone (ZEN) are a group of toxic secondary metabolites produced by certain fungi. They naturally contaminate foods and feeds [1], which lower the product quality, pose severe health risk to humans and animals, and cause profound economic losses worldwide [2].

FB_1 is a mycotoxin produced by the fungus *Fusarium verticillioides*, which commonly infects corn and other agricultural products. *Fusarium* species can also be found in moisture-damaged buildings, and, therefore, exposure of humans to *Fusarium* mycotoxins including FB_1 may take place. The cellular mechanisms behind FB_1-induced toxicity include the induction of oxidative stress, apoptosis, and cytotoxicity, as well as alterations in cytokine expression. The effects of FB_1 on different parameters vary markedly depending on what types of cells are studied or what species they originate from. These aspects are important to consider when evaluating the toxic potential of FB_1 [3–5]. Several studies have indicated that FB_1 is a hepato-carcinogen in BD IX rats; another study reported on its nephro-carcinogenicity in Fischer rats and liver of B6C3F1 mice [6]. A presence of FB_1 in corn is associated with an increase in the incidence of esophageal [7] and liver [8] cancers in humans. Pocsfalvi et al. [9] studied Fusarium mycotoxins and their possible noncovalent interaction with DNA it was found that fusaproliferin similarly to beauvericin forms weakly bound complexes with various oligonucleotides. The formation of such adducts is specific for both single- and double-stranded oligonucleotides but is not specific for a determined sequence or base type. These suggest an electrostatic type of interaction between the negatively charged sugar-phosphate backbone and the fusaproliferin molecule. FB_1 also investigated in the same manner and no adduct formation could be detected, suggesting the lack of noncovalent interaction with DNA for this mycotoxin [10]. Klaric et al. [11] reported that FB_1 is genotoxic to in Porcine Kidney PK15 Cells, showing predominant clastogenic effects. This myctoxin is effective in relatively low concentrations, its effects might also occur in animals and humans following the consumption of mycotoxin contaminated feed and food.

Lu et al. [12] developed an electrochemical immunosensing method for detection of FB_1 and DON. The screen printed carbon electrodes (SPEs) used as working electrode. The SPEs modified by gold nanoparticles (AuNPs), polypyrrole (PPy) and electrochemically-reduced graphene oxide nanocomposite film for sensitive detection of two mycotoxins. Yang et al. [13] designed an electrochemical immunosensor for detecting FB_1 in corn using the single-walled carbon nanotubes/chitosan surface. The detection mechanism of immunosensor based on an indirect competitive binding to a fixed amount of anti-FB_1 between free FB_1 and FB_1-bovine serum albumin, which conjugated on covalently functionalized nanotubes/chitosan laid on the glassy carbon electrode.

The FB_1 detection techniques, e.g., an immunochromatographic assay [14], thin layer chromatography (TLC) [7], enzyme-linked immunosorbent assay (ELISA) [15–17], a lateral flow immunoassay [18], fluorescence resonance energy transfer based methods [19], aptamer based sensors [20–23], and immunosensors [12–14,18,19,24–26] are

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expensive, complicated, hardly employed and time consuming for on-site measurement.

The electrochemical detection techniques have more advantages such as, time saving, simple analysis by offering specific recognition process and requiring small amount of sample. At this point, electrochemical techniques offer to obtain reliable and fast response, to achieve sensitive and selective detection and to miniaturize fabricated biosensors [27–32]. Electrochemical impedance spectroscopy (EIS) technique can provide information on the impedance changes before and after biointeraction process at the electrode surface, which is mainly based on the change of the charge transfer resistance (Rct) using a redox couple. Due to its high sensitivity and label-free characteristics, there has been a growing attention on impedimetric detection of various types of biointeractions [33–37].

To our best knowledge, this is the first study in the literature, which presented the impedimetric detection of in-situ interaction between mycotoxin, Fumonisin B1 and fsDNA in our study by using pencil graphite electrode (PGE). The experimental conditions; such as, fsDNA concentration, FB_1 concentration and interaction time were firstly optimized. The selectivity of the impedimetric DNA biosensor to FB_1 was tested in the presence of mixture samples containing FB_1 and each of other mycotoxins, such as ZEN, DON.

2. Materials and methods

2.1. Apparatus and chemicals

All impedimetric measurements were carried by using AUTOLAB – PGSTAT 302 (NOVA) electrochemical analysis system supplied with a FRA 2.0 module (Eco Chemie, The Netherlands). The three electrode system was consisted of the pencil graphite electrode (PGE), an Ag/AgCl/KCl reference electrode and a platinum wire as the auxiliary electrode. The electrochemical impedance spectroscopy (EIS) measurements were performed in the Faraday cage (Eco Chemie, The Netherlands). The mycotoxins: Fumonosin B1 (FB1), zearalenone (ZEN), deoxyvinalenol (DON) and fish sperm DNA were purchased from Sigma (Germany).

The stock solutions of fish sperm double stranded DNA (fsDNA) (1000 μg/mL) were prepared in Tris–EDTA buffer solution (10 mM Tris–HCl, 1 mM EDTA, pH: 8.00; TE) and kept frozen. More dilute solutions of fsDNA were prepared in 0.5 M acetate buffer containing 20 mM NaCl (ABS; pH 4.80). According to the preparation of the solution of FB_1 as well as other mycotoxins, the procedure was followed that was previously reported by our group [38]. The stock solution of Fumonisin B1 as 50 μg/mL was prepared in acetonitrile. The diluted FB1 solutions were prepared freshly in 0.05 M phosphate buffer solution (PBS; pH 7.40). ZEN was prepared in DMSO and its diluted solutions were prepared in PBS. The stock solutions of DON were prepared in acetonitrile and its diluted solutions were prepared in PBS [38].

Other chemicals were in analytical reagent grade and they were supplied from Sigma and Merck. All stock solutions were prepared using deionized and autoclaved water.

2.2. Preparation of DNA modified PGE

Firstly, the PGEs were electrochemically pretreated by applying +1.40 V for 30 s in ABS. Each pretreated graphite lead was immersed into vials containing 100 μL of fsDNA solution for immobilization process via passive adsorption onto PGE surface during 10 min. Each of the graphite electrodes was then rinsed with ABS for 10 s to remove unbound DNA [37]. Impedimetric measurement was performed in the following section given below.

2.3. The surface-confined interaction of FB_1 with fsDNA

DNA immobilized PGEs were immersed into the vials containing 100 μL solution of FB_1 during 1, 3, 5, 15 and 30 min for surface confined interaction process and then, the electrodes were rinsed respectively using a PBS. The schematic representation was presented in Fig. 1.

2.3.1. Interaction of FB1 with DNA in mixture sample containing each of other mycotoxins

In order to examine the selectivity of impedimetric sensor to FB1, DNA immobilized electrodes were immersed into the vials containing 100 μL of the mixture solution FB_1:ZEN or FB_1:DON as (1:1) for interaction process, and the electrodes were then rinsed with PBS for 10 s.

2.4. Preparation of FB_1 modified PGE

For control experiment, the pretreated graphite electrode was immersed into vials containing 100 μL of FB_1 solution for immobilization through by passive adsorption onto the electrode surface. FB_1 modified PGE was then rinsed by using PBS.

2.5. Impedance measurements

The EIS measurements were performed in the presence of 2.5 mM $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ (1:1) mixture as redox probe prepared in 0.1 M KCl. The impedance was measured in a frequency range from 10 mHz to 1000 kHz at the open circuit potential of +0.23 V versus Ag/AgCl with a sinusoidal signal of 10 mV. The respective semicircle diameter corresponds to the charge transfer resistance (R_{ct}), the values are

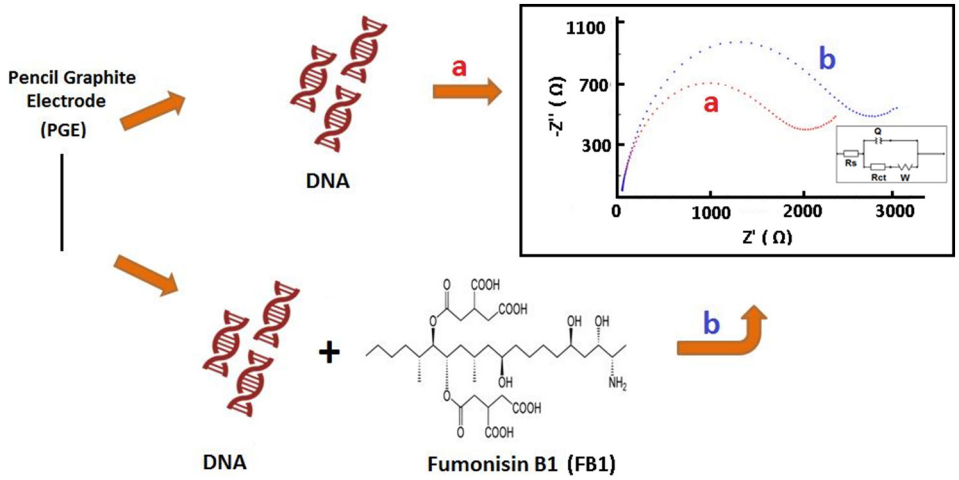

Fig. 1. The representative impedimetric detection (a) fsDNA modified PGE, (b) after interaction between FB_1 and fsDNA at PGE surface.

calculated using the fitting program AUTOLAB PGSTAT 302 (FRA version 4.9, Eco Chemie).

3. Results and discussion

First of all, we optimized the concentration of fsDNA that was immobilized onto the electrode surface in order to obtain full coverage surface with optimum DNA concentration. The Nyquist diagram (Fig. 2A) and related histograms (Fig. 2B) were given in Fig. 2 in order to present the effect of fsDNA concentration varying in the range of 2.5–12.5 μg/mL upon to the electrode response (i.e., the charge transfer resistance at the electrode-electrolyte interface-Rct). The values of Rct, W, Rs and Q were recorded for PGE and DNA modified PGE.

The average Rct value obtained by unmodified PGE as well as fsDNA modified PGE after immobilization of DNA in various concentrations from 2.5 μg/mL to 12.5 μg/mL onto electrode surface was calculated and found to be 110.56 ± 23.53 Ohm (RSD %, 21.29%, n = 3), 686.67 ± 133.82 Ohm (RSD %, 19.49%, n = 3), 1121.40 ± 121.06 (RSD %, 10.86%, n = 3), 1492.57 ± 336.33 (RSD %, 22.53%, n = 3), 1948.67 ± 250.65 Ohm (RSD %, 12.86%, n = 3) and 1606.50 ± 491.31 (RSD %, 26.10%, n = 3) respectively. According to these results, it was concluded that the Rct value increased till 10 μg/mL DNA after then it decreased (Fig. 3). Thus, 10 μg/mL DNA was chosen as the optimum concentration with a good repeatability in our further experiments.

The detection limit (DL) was estimated in the linear concentration of DNA varying from 2.5 to 10 μg/mL (Fig. S1) according to method described by Miller and Miller [39], and it was found to be 0.10 μg/mL with a regression equation y = 166.29x + 273.04 with R^2 = 0.99.

Next, the effect of FB_1 concentration upon the Rct value was examined by PGE in various FB_1 concentrations; varying from 10 ng/mL to 50 ng/mL and accordingly, the results were shown in Fig. 4. The average Rct values were measured as 359.80 ± 71.43 μA (RSD%, 19.85%, n = 3),

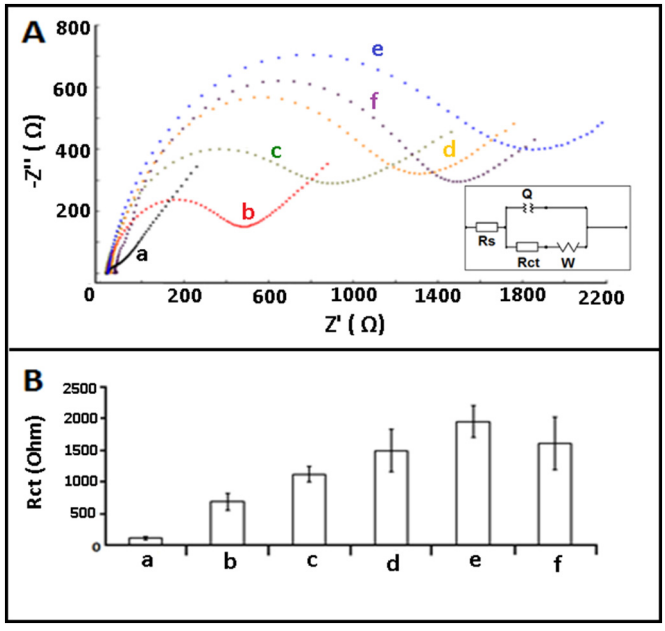

Fig. 2. The effect of DNA concentration upon to the response: (A) Nyquist diagrams and (B) histograms representing Rct values obtained (a) PGE in different concentrations of fsDNA (b) 2.5 μg/mL (c) 5 μg/mL, (d) 7.5 μg/mL, (e) 10 μg/mL, (f) 12.5 g/mL in the presence of 2.5 mM $K_3[Fe(CN)_6]/K_4[Fe(CN)_6]$ (1:1) mixture as redox probe prepared in 0.1 M KCl. Inset was the equivalent electrical model used to fit the impedance data. The impedimetric results were fitted by using an equivalent circuit model, R(Q(RW)) the parameters of which are listed in the text; R_S is the solution resistance. The constant phase element Q is then related to the double layer capacitance at the electrode-electrolyte interface. R_{ct} is related to the charge transfer resistance at the electrode-electrolyte interface. The constant phase element W is the Warburg impedance due to mass transfer to the electrode surface.

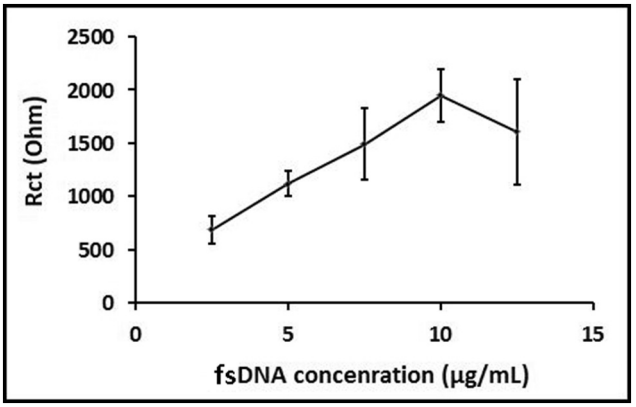

Fig. 3. The graph obtained from Rct values measured in the presence of different concentrations of fsDNA varying from 2.5 to 12.5 μg/mL.

425.75 ± 55.13 μA (RSD%, 12.95%, n = 3), 465.00 ± 65.32 μA (RSD%, 14.05%, n = 3), 519.00 ± 110.62 μA (RSD%, 21.31%, n = 3), 505.80 ± 109.46 μA (RSD%, 21.64%, n = 3), respectively. An increase at the Rct value was recorded till 40 ng/mL of FB_1 then it leveled off (Fig. 5). The highest increase at Rct (i.e., approximately 5-fold-increase) was recorded after immobilization of 40 ng/mL FB_1 onto PGE (shown in Fig. 4). An increase at Rct value means that there was a decrease at electrical conductivity of electrode surface due to the immobilization of FB_1 onto the electrode surface.

The detection limit of FB_1 was calculated in a linear concentration range of toxin (shown in Fig. S2) by using the regression equation y = 5.15x + 313.18 with R^2 = 0.99 and it was found to be 3.69 ng/mL. According to the results, the optimum FB_1 concentration value was chosen as 40 ng/mL resulting with a higher binding capacity of toxin onto the surface of PGE.

There have been several studies presenting the detection of FB1 using different methods and some of these studies were summarized in Table 1. In comparison to the previous reports, our impedimetric assay developed for toxin detection was found as cost-effective and selective assay in contrast to the earlier reports performed by using

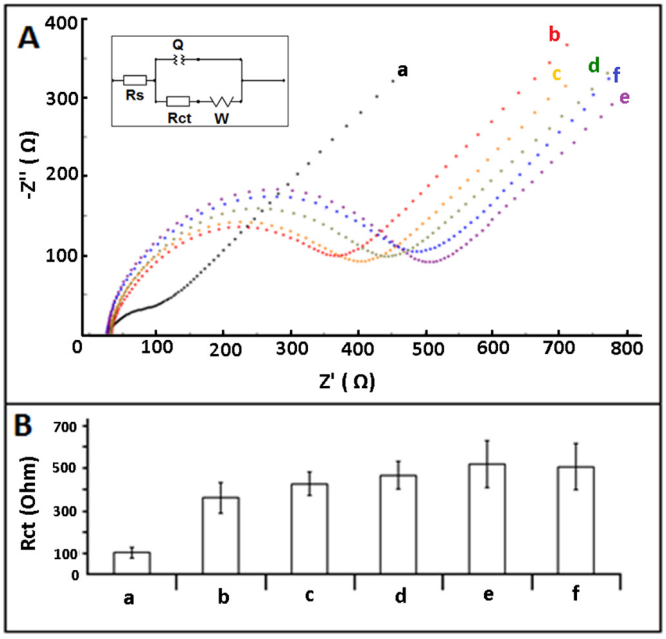

Fig. 4. The effect of FB_1 concentrations upon to the response: (A) Nyquist diagram and (B) Histograms representing Rct values obtained before (a) and after FB_1 immobilization onto PGE surface in different FB_1 concentrations (b) 10 ng/mL, (c) 20 ng/mL, (d) 30 ng/mL, (e) 40 ng/mL, and (f) 50 ng/mL.

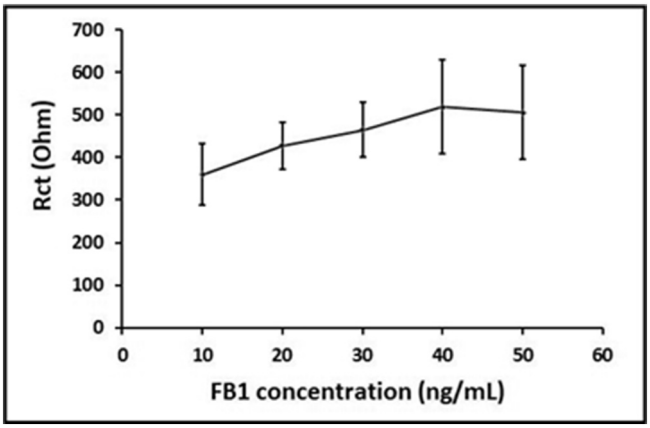

Fig. 5. The line graph obtained from Rct values measured in the presence of different concentrations of FB_1 varying from 10 to 50 ng/mL.

aptamer based sensors [20–23], immunosensors [12–14,18,19,24–26], screen-printed electrodes [12], AuNPs modified electrodes [12,18,22,25] and SPR sensors [40].

The electrochemical behaviour of surface was also investigated impedimetrically before/after immobilization of DNA onto electrode surface as well as in the absence/presence of interaction between FB_1 and DNA at PGE surface. The average Rct values of PGE, FB_1/PGE, DNA/PGE and FB_1/DNA/PGE were measured as 110.56 ± 23.56 Ω (RSD %, 21.29%, n = 3), 519.00 ± 110.62 Ω (RSD %, 21.31%, n = 3), 1948.67 ± 250.65 Ω (RSD %, 21.86%, n = 3) and 2684.88 ± 389.79 (RSD %, 14.52%, n = 3) respectively. After interaction with FB_1 with DNA modified PGE, 40.18% increase at Rct was recorded (Fig. 6b to d). This increase is consistent with the fact that the FB_1 interacts with DNA resulting with a decrease at the conductivity of PGE surface, since there is an decrease at the interfacial electron transfer occurred between the electrode and the electroactive species in solution [31,32]. After interaction of FB1 with DNA, an increase was obtained at the resistance due to an increase at the negativity of electrode surface due to the electrostatic type of interaction occurred between fumonosin B1 and the negatively charged sugar-phosphate backbone of DNA [9].

The effect of interaction time upon to biosensor response was also investigated under the optimum concentration of fsDNA and FB_1 (i.e., 10 μg/mL fsDNA and 40 ng/mL FB_1) in various interaction time; such as, 1, 3, 5, 15, 30 min. Accordingly, the results were shown in Fig. 7. In the presence of 3 min interaction time of FB_1 with DNA, the average Rct value was measured as 2684.88 ± 389.73 Ω (RSD % = 14.52%, n = 3). The highest increase was

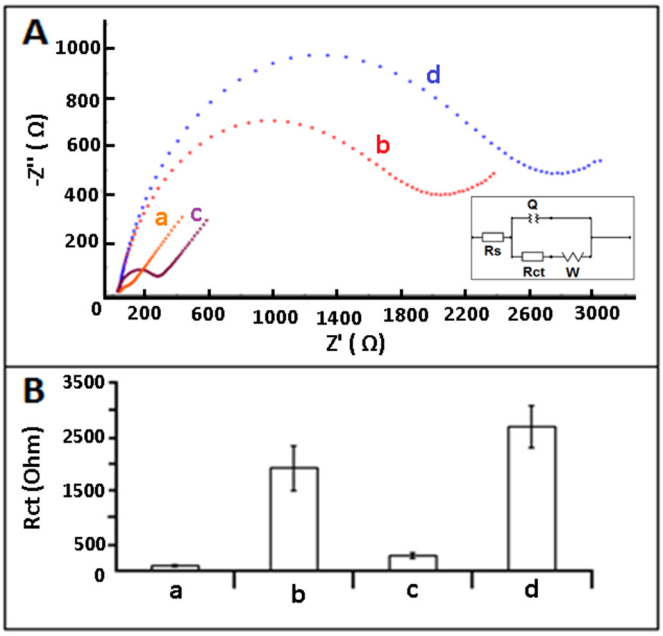

Fig. 6. (A) Nyquist diagrams of (a) PGE, (b) DNA/PGE, (c) FB_1/PGE, (d) FB_1/DNA/PGE in 2.5 mM $Fe(CN)_6^{3/4}$. (B) Histograms representing the average Rct values (n = 3) of (a) PGE, (b) DNA/PGE, (c) FB_1/DNA, (d) FB_1/DNA/PGE.

obtained in 3 min interaction time of all, that was 1.4 times higher than the DNA modified PGE as 1915.00 ± 415.88 Ω (RSD % = 21.68%, n = 3). Hence, 3 min interaction time was used as optimum interaction time in our further experiments.

The selectivity of the impedimetric biosensor to FB1 was tested in the mixture samples containing ZEN-FB1 (1:1) or DON-FB1 (1:1) and the results were presented in Fig. 8. The average Rct values of DNA modified PGE, FB_1/DNA/PGE, ZEN:FB_1/DNA/PGE and DON:FB_1/DNA/PGE were measured as 1830.98 ± 420.99 Ω (RSD %, 22.99%, n = 3), 2555.57 ± 416.81 Ω (RSD %, 16.31%, n = 3), 2265.00 ± 385.32 (RSD %, 17.01%, n = 3) and 2244.00 ± 565.16 (RSD %, 25.19%, n = 3) respectively. According to the results, the highest R_{ct} value with an increase ratio (39.57%, shown in Fig. 8b) was determined after interaction of FB1 with DNA of all. On the other hand, 23.70% and 22.56% increase at the Rct value was obtained in the presence of mixtures samples of FB_1 with ZEN and DON, respectively after in-situ surface confined interaction with DNA. Hence, our impedimetric DNA biosensor showed a selective behavior to FB_1 even in the mixture sample of FB_1 with each of other toxins; ZEN and DON.

Table 1
Recent studies developed for FB1detection comparison to the present study. Abbreviations: electrodes: SPE: screen printed electrode, GCE: glassy carbon electrode, PGE: pencil graphite electrode, modification materials: MB: molecular beacon, PDMA: poly(2,5-dimethoxyaniline), MWCNT: multi-walled carbon nanotube, SWCNT: single-walled carbon nanotube, CHIT: chitosan, GRP: graphene, GONCs: graphene oxide nanocolloids, TiO_2: titanium dioxide, PPy: polypyrrole, ERGO: electrochemically reduced graphene oxide, method: FRET: fluorescence resonance energy transfer, TLC: thin layer chromatography, ELISA: Enzyme-Linked ImmunoSorbent Assay, DPV: differential pulse voltammetry, EIS: electrochemical impedance spectroscopy.

Method	Electrode	Detection limit	References
DPV	Anti-FB1/AuNPs/PPy/ERGO/SPE	4.2 ppb	[12]
DPV	Anti-FB1/SWCNT/CHIT/GCE	2 pg/mL	[13]
Immunochromatographic strip	–	5 ng/mL	[14]
Lateral flow immunoassay	AuNP/anti-FB1 modified surface	2 ng/mL	[18]
FRET	AuNP/MB/anti-FB1 modified surface	0.01 ng/mL	[19]
Amperometry	Anti-FB1/AuNP/GRP/thionine	1 pg/mL	[20]
Fluorescence intensity based microarray	FB1 aptamer/TiO_2-porous silicon surface	0.21 pg/mL	[21]
EIS	FB1 aptamer/AuNPs/GCE	2 pM	[22]
EIS	Anti-FB1/PDMA/MWCNT/GCE	3.8 pg/L	[24]
DPV	FB1 aptamer/GONCs	15 nM	[25]
SPR	–	2 μg/kg	[40]
EIS	PGE	3.69 ng/mL	Present study

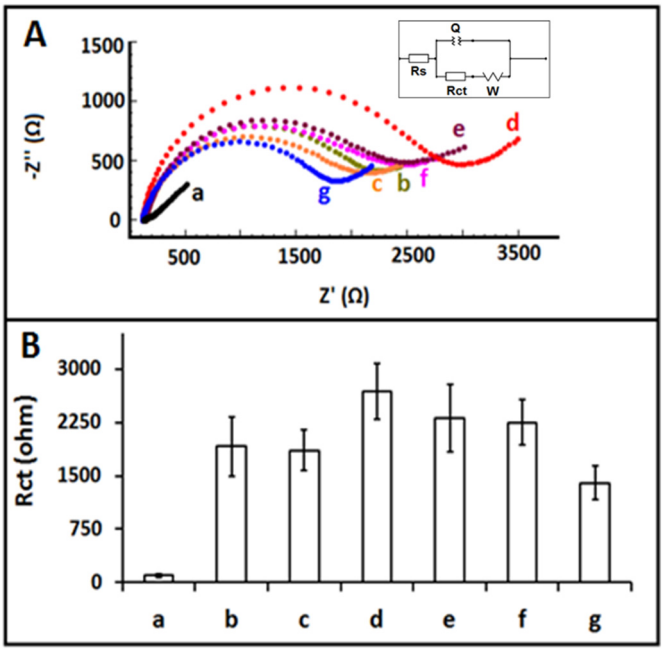

Fig. 7. The effect of FB_1 interaction times with DNA at PGE surface. (A) Nyquist diagram, (B) histograms representing Rct values obtained before/after DNA immobilization onto PGE surface and FB_1–DNA interaction; (a) PGE, (b) DNA modified PGE and after the interaction 40 ng/mL FB_1 with 10 μg/mL DNA for (c)1 min, (d) 3 min, (e) 5 min, (f) 15 min, (g) 30 min interaction time.

4. Conclusion

Fast, selective and sensitive and reliable detection of mycotoxin, FB_1 is very important for human health as well as examining of its biointeraction with nucleic acids since it causes oxidative stress, apoptosis, cytotoxicity and it also damages several tissues such as liver, kidney and brain. The impedimetric detection protocol presented herein a low detection limit as 3.69 ng/mL for FB1 by using PGE in combination with EIS technique. In addition, this study is presenting the impedimetric detection of in-situ interaction between mycotoxin, FB1 and DNA by using PGE for the first time in the literature. Under the optimum experimental conditions, the selectivity of the in-situ interaction of FB_1 with fsDNA was also tested in the presence of mixture samples containing FB_1 and each of other mycotoxins, such as ZEN, DON.

As a conclusion, our impedimetric DNA biosensor presents a great promise furtherly towards to the development of fast, low-cost, selective and sensitive biosensing protocol for monitoring of any type interactions not only toxins, but also biological hazards as well as warfare agents while monitoring its interactions with nucleic acids.

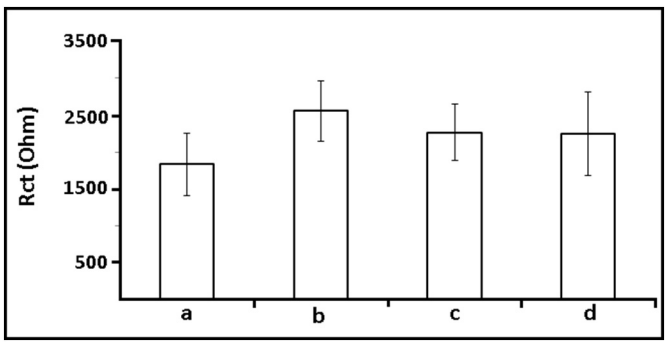

Fig. 8. Histograms presenting the average R_{ct} values (n = 3) obtained (a) before and after the interaction of DNA with (b) 40 ng/mL FB_1 as well as in the mixture of (c) ZEN:FB_1 (1:1), (d) DON:FB_1 (1:1).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijbiomac.2019.08.024.

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