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Curcumin-graphene quantum dots for dual mode sensing platform: Electrochemical and fluorescence detection of APO*e4*, responsible of Alzheimer's disease

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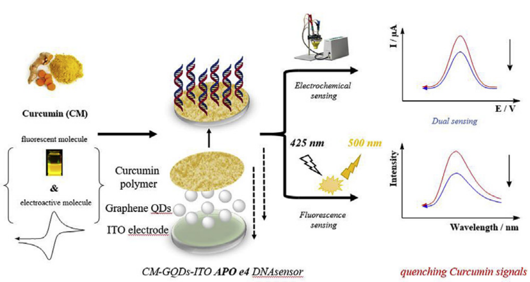
HIGHLIGHTS

- A sensitive dual amperometric and fluorescence Curcumin DNAsensor was developed.
- The LOD was founded to be 0.48 pg.mL^{-1} with a sensitivity of 4.47 nA.mL.pg^{-1}.
- A good metrological performances were demonstrated.
- Human blood plasma was used as real matrix.

GRAPHICAL ABSTRACT



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ABSTRACT

New dual electrochemical and fluorescence sensitive curcumin-graphene quantum dots sensing platform coated on the transparent Indium-Tin-Oxide electrode was developed to sense APO*e4* DNA, responsible of Alzheimer's disease. Curcumin molecule with its dual fluorescence and electrochemical properties was electropolymerized on GQDs-ITO surface. EDC/NHS chemistry was used to covalently immobilize an amino-substituted DNA probe *via* a malonic acid spacer. Quenching of curcumin signals following hybridized DNA complex was employed to quantify APO*e4* DNA. Amperometric studies revealed an ultrasensitive behavior toward the formation of DNA complex with a sensitivity of 4.74 nA.mL.pg $^{-1}$ and a limit of detection as low as 0.48 pg mL $^{-1}$. The platform exhibits very good performances such as repeatability, reproducibility, selectivity and long storage stability. Fluorescence results were established for the support and the complementarity of electrochemical results. Founded results confirmed the ultrasensitivity of platform with comparable performances. Recorded results in human blood plasma demonstrated the high efficacy of curcumin system sensing even in the clinical matrix.

1. Introduction

Several studies demonstrated that APO*e4* allele, one of the three common alleles of apolipoprotein E, recognized as a lipid transport protein, could be the major risk factor for various diseases such as

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coronary artery, Alzheimer's disease, Parkinson and Huntington diseases [1–6]. Recently, numerous techniques were employed to detect APOE in its various biologic structures, citing ELISA, radiative plasmon surface resonance, mass spectroscopy, colorimetric, electrochemical and lateral flow immunoassay [7–9]. Indeed, Ren et al. have constructed a novel point of care testing based colorimetric immunoassay. This developed platform has shown a good performance even at clinical analysis with 0.42 pg/mL limit of detection [10]. Further, Sciacca et al. have developed a rapid label-free clinical sensor based on radiative plasmon surface resonance using silver coated optical fibers. Reported work demonstrates a high rapidity, less than 1 h, with a high specificity toward APOE. In this case, a limit of detection was found to be less than 5 μg/mL [11].

Moreover, Wisniewski et al. have used ELISA technique to quantify the apolipoprotein E [12]. Despite the high sensitivity presented by ELISA, the latter suffers from a mediocre limit of detection and a high analysis time. However, electrochemical technique, characterized by its rapid, sensitive and low cost properties, could be a suitable solution. In literature, numerous works, which have described the employment of electrochemical methods such as amperometric and impedimetric are reported [13–15]. For instance, Arben group has widely used electrochemistry studies to quantify apolipoprotein *e4* protein. Recently, they described the development of a nanobiosensor based on the use of porous magnetic microspheres, PMM, for APO *e4* sensing. Based on the electrocatalytic effect of gold nanoparticles toward hydrogen evolution reaction, formed platform could sense the protein target in different clinical fluids, serum, plasma and CSF, with a limit of detection of 80 pg/mL [16].

On the other hand, Diferuloylmethane ($C_{21}H_{20}O_6$), known as Curcumin (CM), is a bioactive polyphenol component present in the rhizomes of Curcumin longa. Due to its unique biological activities including antioxidant, anti-inflammatory, antiviral, antibacterial and anticancer effects. A recent research shows that CM has a positive impact on Alzheimer disease [17].

CM which has been found non-toxic for human up to 10 g/day shows a potential interest in clinical fields [18–21]. Recently, CM was widely used in fluorescence sensing. Wu et al. have employed curcumin to sense fluoride ions. By forming an anionic complex, it has been demonstrated that high sensitive fluorimetric and colorimetric response has been found following the presence of F^- anion [22]. Further, Wei and collaborators have developed cross-linked fluorescence microspheres, poly (cyclotriphosphazene-co-curcumin, to detect picric acid which is considered as highly explosive than TNT [23]. In addition, Patra et al. have reported the formation of microcapsules (MCs) containing self-assembled nanoparticles formed from poly [diallylammonium chloride-co-(sulfur dioxide)]. This curcumin nanohybrid was served to detect fluorescently the fish sperm DNA as DNA model [24]. However, the electrochemical behavior of curcumin still not well explored until today. In fact, only a few numbers of publications report the electrochemical behavior of curcumin in literature [25–27].

In the present work, we describe the use of the electropolymerized curcumin on GQDs-ITO transparent electrode as a dual electrochemical and fluorometric platform to sense APO *e4*, biomarker protein for several neurodegenerative and artery diseases. DNA probe was covalently attached to curcumin *via* a malonic acid spacer. Amperometric results revealed a high sensitive response toward APO *e4* DNA with a linear range from 20 to 400 pg/mL. A limit of detection of 0.00474 μA mL/pg was reached. A complementary study, fluorescence results showed a comparable sensitivity around 47.58 (a.u). mL/pg. The platform exhibits high metrological performances such as repeatability, reproducibility, selectivity and long storage stability. The system applicability was carried out in clinical fluids such as human blood plasma.

2. Materials and methods

2.1. Apparatus and electrodes

Electrochemical measurements were recorded using a Metrohm Autolab PGSTAT M204 electrochemical workstation (Basel, Switzerland). Experiments were performed at room temperature with a three electrode system composed of platinum wire as an auxiliary electrode, Ag/AgCl as a reference and the modified ITO electrode as a working electrode and data were collected using Nova® v1.11 software.

Fluorescence studies were conducted using a Fluorolog-3 fluorometer equipped with MicroMax 384 microplate reader. SEM images were captured using a MIRA3 LMU Oxford EDX.

2.2. Reagents and solutions

All reagents were of the highest available grade. Curcumin, citric acid, PBS tablet, malonic acid, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), N-hydroxysuccinimide (NHS), cholesterol, HIgG protein, glucose oxidase, ferricyanide and ferrocyanide were purchased from Sigma-Aldrich. 5′-cag-gcg-gcc-gcg-cac-gtc-ctc-3′, 5′-gag-gac-gtg-cgc-ggc-cgc-ctg-3′ and 5′-gag-gac-gtg-tgc-ggc-cgc-ctg-3′ were obtained from biomers. EIS measurements were carried out using 50 μL of phosphate-buffered saline solution (0.1 mM, pH 7.4) containing a mixture of 5 mM $Fe(CN)_6^{4-}$ and 5 mM of $Fe(CN)_6^{3-}$ was used as a redox probe couple. All experiments have been done at least in triplicate using different the platforms.

2.3. Graphene quantum dots preparation

Graphene quantum dots were prepared according to the literature [28]. Briefly, 2 g of citric acid was heated in a beaker for approximately 20 min at 200 °C until the solution becomes deep orange. After that, 100 mL of 0.1 mg mL^{-1} NaOH solution was dropped in the obtained orange liquid. A neutralisation procedure to pH 7.0 has been necessary using an HCl solution to obtain required GQDs.

2.4. Fabrication of GQDs-Curcumin biosensor

Based on step-by-step strategy, GQDs-Curcumin DNA sensor was developed in a few steps (Fig. 1). Firstly, it is worth to mention that ITO electrode required a pre-treatment cleaning process to avoid contamination adsorption [29]. To adsorb GQDs on surface, ITO active surface electrode was coated with 50 μL of GQDs solution. Then, curcumin was immobilized on treating GQDs-ITO surface *via* an electropolymerisation process. Briefly, the modified surface was incubated into 50 μM curcumin in freshly prepared PBS (pH 8) solution and 20 consecutive voltammetric cycles were performed in the potential range of 0.1–0.6 V at the scan rate of 50 mV/s. Then, EDC/NHS chemistry was employed to Bioconjugate, with amino-terminated DNA probe, CM-GQDs-ITO modified surface throw malonic acid spacer. By this method, CM-GQDs-ITO surface underwent an activation process by incubating into 0.5 mM EDC/NHS solution. In order to block unreacted groups of modified surface and to avoid non-specific adsorption of DNA target, modified DNA surface was incubated in 1% of BSA solution was for 30 min. Developed CM-GQDs DNA sensors were dried under nitrogen and stored at 5 °C to further hybridization process.

2.5. Dual amperometric and fluorescence sensing

Hybridization process of CM-GQDs DNA sensor was monitored by electrochemical and fluorescence methods. Indeed,

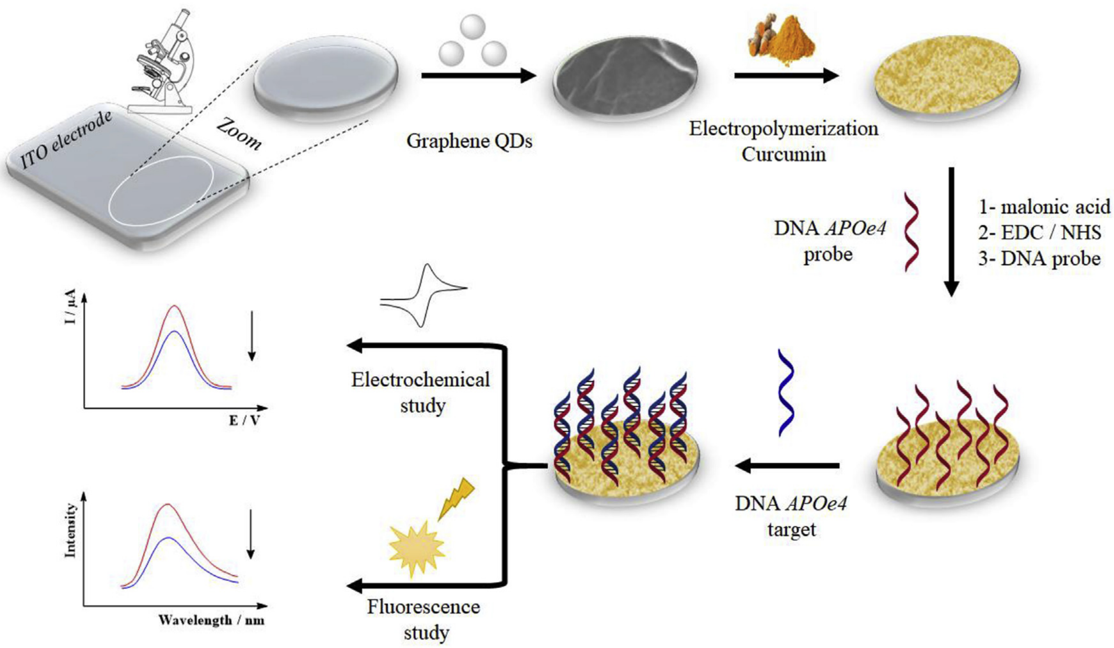

Fig. 1. Schematic representation of the stepwise procedure to prepare GQDs-Curcumin APO*e4* DNA sensor.

amperometric measurements were carried out in an electrochemical cell containing 5 mL of 1 mM PBS buffer. Further, fluorescence results were obtained by measuring fluorescence signals of dried transparent CM-GQDs-ITO DNA sensor applying 425 nm excitation wavelength.

3. Results and discussion

3.1. CM-GQDs-ITO DNA sensor design

Curcumin coated graphene quantum dots-ITO electrode was obtained via step-by-step strategy. In fact, GQDs have been used to modify ITO electrode due to their unique electronic properties especially in the considerable enhancement of electron transfer rate [30]. Further, curcumin as a dual electrochemical and fluorescent transducer was immobilized on the modified surface through electrochemical polymerisation reported by Devadas et *al.* on the carbon electrode [26]. To bioconjugate the modified electrode and enhance the biological response of platform, covalent bonds were used based on EDC/NHS chemistry. In order to characterize and prove the stability of the developed platform, electrochemical, microscopic and spectroscopic techniques were employed.

3.1.1. Microscopic and spectroscopic studies

In this work graphene quantum dots as electrocatalytic electron transfer rate nanomaterials were prepared as described previously. The surface morphology of GQDs modified ITO electrode was elucidated through scanning electron microscopy. SEM images, before and after modification, confirm the adsorption of GQDs on ITO surface. Fig. 2a reveals the presence of a three-dimensional wrinkled layer in the ITO surface exhibited by the presence of GQDs on ITO electrode. This observation was also confirmed by AFM technique where the wrinkles are more than 8 nm (inset Fig. 2a). On the other hand, GQDs were characterized by transmission electron microscopy, fluorescence and FTIR spectroscopies (Fig.S1). As seen in Fig.S1a, FTIR spectrum showed the presence of all characteristic bands of GQDs such as 2980 cm^{-1} representing C–H bonds and 1393 cm^{-1} exhibited by the presence of the $-CO_2$ groups. Fig. S1b showed the presence of a maximum emission wavelength localized at 370 nm related to the aqueous GQDs solution. Moreover, the formation of curcumin film as fluorescent transducer was confirmed by fluorescence study. For this reason, dried CM-GQDs-ITO electrode was analysed and the fluorescent spectrum reveals the presence of a maximum of emission at 500 nm related to the immobilized curcumin molecules (Fig.S2).

3.1.2. Electrochemical studies

As a dual electrochemical and fluorescence transducer, electropolymerized curcumin on GQDs-ITO electrode was also characterized with electrochemical techniques such as cyclic voltammetry, differential pulse voltammetry and electrochemical impedance spectroscopy. It is worth to declare that no considerable curcumin electrochemical signal was observed on bare ITO electrode. However, the presence of GQDs on ITO surface enhance significantly the electroactivity of CM because of it-wrinkled surface, which was rich with active carboxylic sites allowing the creation of the hydrogen bond with curcumin molecules (Fig. 2. b). Furthermore, B. Devadas et al. were described the electrochemical mechanism of the polymerisation of CM on carbon electrode [26]. They reported that electropolymerisation event was controlled by nucleophilic reaction between the two groups, 3,5 dione and o-quinone, with the functionalized sites presented on active GQDs-ITO electrode surface. Furthermore, recorded CV of CM-GQDs-ITO electrode in PBS solution (pH7) revealed the presence of quasi-reversible redox signal related to the electro-activity of curcumin modified GQDs-ITO electrode. To confirm the immobilization of CM on the electrode surface, scan rates study was developed (Fig.S3). Fig. 2c showed the dependence of the logarithm of the oxidation current of CM with the logarithm of the respective scan rates. The plot showed a straight line with a slope near from the unity indicating an adsorption control. Moreover, DPV voltammogram revealed that the oxidation current of the immobilized curcumin on modified electrode is localized at 0.12 V (inset Fig. 2c). In the other hand, Fig. 2d exhibits the Niquist plots of the different stepwise of electrode modification. In fact, coating ITO electrode with GQDs

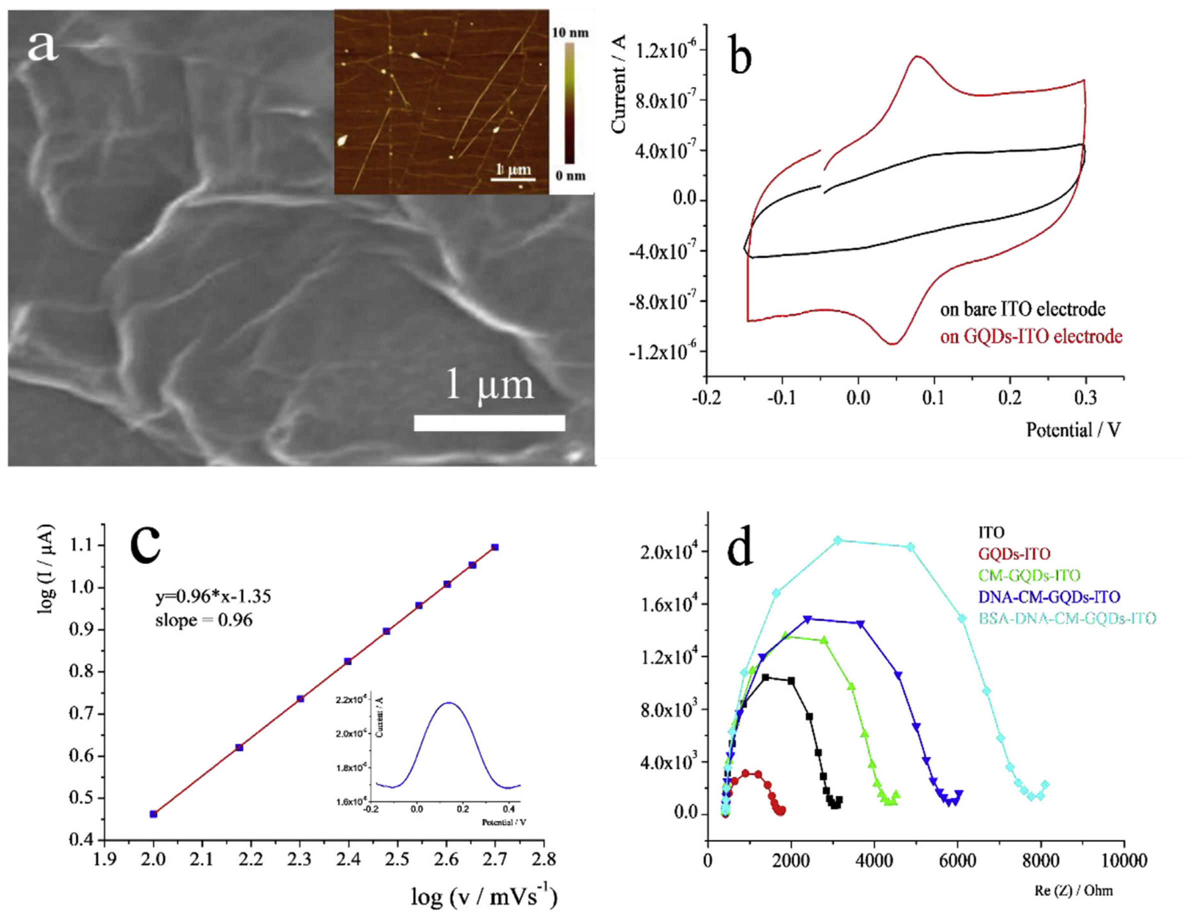

Fig. 2. SEM image of modified GQDs-ITO electrode (inset: AFM image of GQDs) (a), cyclic voltammetry of 50 M curcumin recorded in PBS (pH7) at 50 mVs^{-1} scan rate (b), the plot of the logarithm of the oxidation currents of immobilized CM on GQDs-ITO electrode versus the logarithm of various used scan rates (inset: recorded DPV of modified CM-GQDs-ITO electrode in PBS solution and Niquist plots of modifications stepwise (d).

induced a significant decrease in the charge transfer resistance (R_{ct}) due to the high conductivity of graphene structures compared to ITO surface. However, the electropolymerisation of curcumin as well as the bioconjugation step of modified CM-GQDs-ITO exhibited dramatically an enlargement in the semi-circle arc leading to a considerable increase in resistance electron transfer.

3.2. Dual sensing of APOe4 DNA target

Based on the dual functionality of curcumin as an electrochemical and fluorescent transducer and to the transparent property of ITO electrode, electrochemistry and fluorescence, as complementary techniques, were used to quantify APO*e4* DNA on the same studied platforms. Regarding the electrochemical studies, the developed CM-GQDs-ITO DNA sensors were incubated in various APO*e4* DNA concentrations. Recorded DPVs in PBS solution (pH7) revealed a proportional decrease in the oxidation current of immobilized CM (inset Fig. 3a). As expected, the amperometric response decreased linearly with the increase of the APO*e4* DNA. According to Qui et al. [31,32] and Rather et al. [33], the decrease in current can be attributed to the formation of DNA complex acting as an inert kinetic barrier for the electron-transfer of curcumin. Further, the correlation curve of the measured oxidation current versus the APO*e4* DNA concentrations showed a linear response ($R^2 = 0.998$) in the range of 20–400 pg/mL with a sensitivity of 4.74 nA mL/pg (Fig. 3a). An estimated LOD (3 times the standard deviation of the current values obtained for 10 independent amperometric measurements in the absence of DNA target) was found to be 2.18 pg mL^{-1}. Moreover, recorded fluorescence studies, developed on previously electrochemical treated electrodes, revealed a sensitive response toward the presence of various APO*e4* DNA concentrations (Fig. 3b). The observed decrease in the fluorescence response of CM-GQDs-ITO DNAsensor could be related to the quenching of the photoelectron transfer process induced by the formation DNA complex [34]. Further, **inset** Fig. 3b exhibits a linear dependence in the range of 45–400 pg/mL with a sensitivity of *c. a.* 47.58 a. u.mL/pg comparable to that found with electrochemical methods. LOD of fluorescence sensing has been estimated to be 12.4 pg mL^{-1}.

3.3. Analytic performances

3.3.1. Repeatability and reproducibility

To prove the applicability of performed system, repeatability, reproducibility, as well as storage test, were studied. By measuring, 20 times in one single day, the response of CM-GQDs-ITO DNA sensor in the presence of 100 pg/mL of APO*e4* DNA, RSD value was calculated to be 3.1%. Further, the developed platform showed a high reproducibility with a 3.6% RSD value.

Furthermore, three electrodes, which showed the best reproducibility, were stored at 4 °C for one month. Daily recorded studies revealed a decrease by only 7.3%, indicating the great stability of platforms. (Fig.S4).

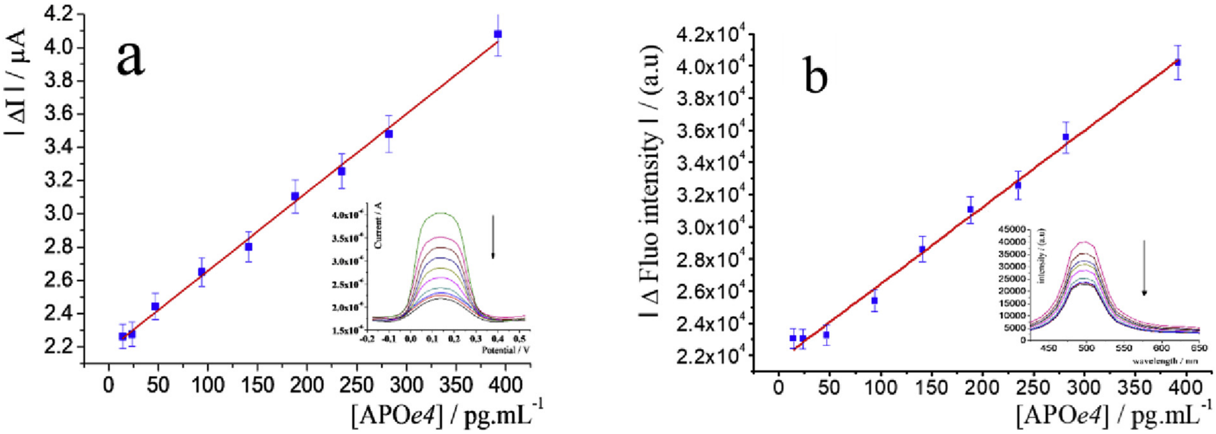

Fig. 3. Correlation curves of the dual detection of APO*E4* (insets: analytic responses toward the presence of DNA APOE4 target), electrochemical (a) and fluorescence response (b).

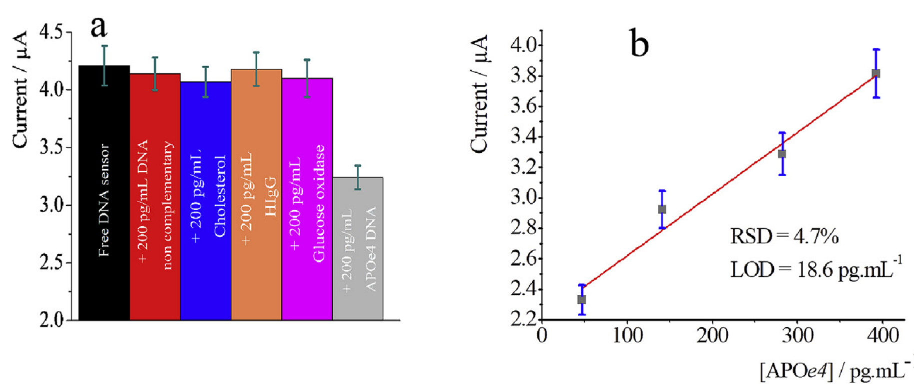

Fig. 4. Histogram of obtained selective results (a) and correlation curve of recorded real test in human blood plasma (b).

Table 1
Reported works on the detection of APO*e4* in its various biological structures (protein and DNA).

Techniques	Platforms	LOD	References
Dual (Impedance/SPR)	ITO-AuNPs-DNA	512 and 286 nM	X.R. Cheng, 2014
Amperometry	ITO-AuNPs-APOE immunosandwich	0.3 ng/mL	Y. Liu, 2015
Chronoamperometry	MB-anti.APOE-APOE-IrO2NP	68 ng/mL	R. Lourdes, 2014
Amperometry	On-chip immunosandwich	12.5 ng/mL	M. Medina-Sanchez, 2014
ELISA	ELISA Kit immunosandwich	–	H. Fukumoto, 2003
Dual (Fluorescence/amperometry)	ITO-GQDs-CM-APOE DNA	2.18 and 12.4 ng/mL	This work

3.3.2. Interference study and real detection in human plasma

Knowing that clinical fluids contain several interfering proteins, the necessity to a high selective sensing system had become a key priority. For this reason, a non-complementary DNA sequence, human immunoglobulin G, cholesterol and glucose oxidase were used to demonstrate the selectivity of the dual platform. Founded results revealed a high sensitivity toward APO *e4* DNA even in the presence of 100 folds of interfering DNA protein amount (Fig. 4a). (For selectivity results see Fig.S5) Furthermore, human blood plasma was chosen to release the real test. In order to avoid clotting which will deplete APO*e4* DNA in plasma. Fibrinogen in plasma sample was pre-removed with ammonium sulfate precipitation. Pre-treated human blood plasma was diluted then 100-fold with Tris-HCl buffer. Developed results exhibited a high sensitive recognition of APO*e4* DNA, which demonstrated the efficacy of the dual CM-GQDs-ITO DNA sensor (Fig. 4b).

3.3.3. Comparative study

Numerous studies, reported in the literature, have described the detection of the APOe4 allele in its various biomarkers. To position our work, we tried to compare it with others (Table 1).

4. Conclusion

Herein, we described a sensitive dual electrochemical and fluorescence detection of APO*E4* DNA, especially responsible on Alzheimer and artery coronary diseases. Knowing by its high sensitive fluorescence response, curcumin molecule was used as a dual sensing transducer. The electrochemical response of this latter was considerably enhanced by the employment of graphene quantum dots. Electrochemical and fluorescence studies of the developed platform in the presence of different APO*e4* DNA target showed a sensitive decrease in analytic responses. The recorded quenching signals were attributed to the formation of DNA complex that blocks the photo-electron transfer process. Analytic performance revealed a high selectivity, stability and efficacy of the formed curcumin-GQDs system. The applicability of the dual DNA sensor was also investigated in the clinical fluid. The recorded results showed a high sensitivity response toward DNA target even in human blood plasma with a good RSD c. a. 4.7%.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.aca.2018.06.075.

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