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1 **Functionalized Electrochemical Aptasensor for Sensing of Ochratoxin A** 2 **in Cereals Supported by *in silico* Adsorption Studies**

3
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10 **Abstract**

11 An aptamer to selectively detect ochratoxin A (OTA) in cereals was developed using silver
12 nanoparticles (AgNPs) in combination with reduced graphene oxide (rGO). As a result of
13 characterization experiments conducted in this study, AgNPs were confirmed to be
14 polydisperse. The electro-catalytic activity was achieved by immobilizing OTA - bovine serum
15 albumin (OTA - BSA) on the rGO/AgNPs substrate. Based on the experimental conditions
16 optimized for the aptasensor, the linear dynamic range was 0.002 to 0.016 mg/L and the
17 threshold was 7×10^{-4} mg/L (S/N = 3). At an atomic and molecular level, computational
18 adsorption studies revealed how the OTA-BSA interacts with the rGO/AgNPs composite
19 substrates on a spatial scale. Calculations using density functional theory (DFT) revealed that
20 OTA has an energy gap of -4.5 eV, which implies a strong tendency to operate as an electron
21 donor. In addition to its excellent reproducibility and good stability, the proposed aptasensor
22 demonstrated its applicability in the food industry.

23 *Keywords: Ochratoxin A, AgNPs, reduced Graphene Oxide, electrochemical aptasensor*

24 _____

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27 1. Introduction

28 Ochratoxin A (OTA) is a metabolite produced by *Penicillium* and *Aspergillus* fungi that
29 structurally consists of a chlorophenolic group containing a dihydroisocoumarin moiety that is
30 linked to L-phenylalanine by an amide bond (**Figure S1A**).^{1, 2} It has a nephrotoxic,
31 immunotoxic, teratogenic, mutagenic and carcinogenic effect in both animals and humans.^{2, 3}
32 As a common food contaminant, it enters the human body through the ingestion of
33 inappropriately stored food products, such as alcoholic products, dried fruits, corn, coffee,
34 spices and cereal products.⁴⁻⁹ It is generally accepted that OTA is known to possess
35 carcinogenic effects as stipulated by the International Agency for Research on Cancer
36 (IARC).¹⁰ For this reason, as part of the established regulations for OTA in foodstuffs, the
37 European Commission established the maximum OTA levels for various foods such as spices
38 (15-20 $\mu\text{g kg}^{-1}$), cereal products (3 $\mu\text{g kg}^{-1}$), dried fruits (10 $\mu\text{g kg}^{-1}$), soluble coffee (10 $\mu\text{g kg}^{-1}$),
39 baby foods (0.5 $\mu\text{g kg}^{-1}$) and grape juices (2 $\mu\text{g kg}^{-1}$).¹¹⁻¹⁶ Many different analytical
40 techniques are available for the detection of OTA. They include high performance liquid
41 chromatography (HPLC)¹⁷ thin layer chromatography (TLC),¹⁸ liquid chromatography-mass
42 spectroscopy (LC-MS),¹⁹ gas chromatography-mass spectroscopy (GC-MS)²⁰ and enzyme-
43 linked immunosorbent assays (ELISA).²¹ Each of these generally acceptable methods has a
44 limitation, such as low sensitivity, low limits of detection and the need for skilled personnel
45 with expertise to handle high-end instrumentation. Notably they are costly, time-consuming
46 and unable to meet the modern-day requirements with high selectivity, good precision, rapid
47 analysis that is cost effective and easy to operate.

48 Aptamers are single-stranded DNA or RNA oligonucleotide fragments that bind to targets such
49 as proteins, cells, small ions and molecules. These oligonucleotides are attained by an *in vitro*
50 Darwinian method called single evolution of ligands by exponential enrichment (SELEX).²²
51 They have gained widespread recognition as probes for biomolecular detection, due to their
52 convenient automated synthesis, high selectivity, stability, adaptable target binding and
53 flexible modification with a variety of functional groups over antibodies.^{23, 24} In recent years,
54 several aptamer-based detection techniques for OTA including fluorescence,²⁵ colorimetry,²⁶
55 chemiluminescence²⁷ and electrochemistry²⁸ have been reported. There is increasing evidence
56 which proves that the detection of OTA using electrochemical aptasensors is a powerful
57 technique, due to fast response, high sensitivity, on-site testing platforms, low background
58 noise, and good reproducibility.^{29, 30} In a recent study by Lv and Wang 2020, they focused on

59 the signal amplification technologies applied to OTA electrochemical aptasensors and
60 highlighted the current limitations and future challenges.³¹ However, to design smart sensing
61 for mycotoxins, it is crucial to synthesise highly efficient working electrode materials. As a
62 result of their large specific surface areas, fast electron transfer, and high density of active sites,
63 noble metal nanoparticles attract considerable research interest.³² Specifically, AgNPs display
64 an interesting quantum characteristics, large surface area, small particle diameter and it has the
65 ability to transfer electron fast.³³ Therefore, AgNPs is widely used in the design of
66 nanocomposites for electrochemical sensors.¹ Currently, numerous nanomaterials, such as
67 carbon nanotubes (CNTs), noble metal nanoparticles and graphene oxide (GO) has been used
68 to fabricate electrochemical sensors.³⁴⁻³⁶ Previous reports revealed that GO and reduced
69 graphene oxide (rGO) has been the key to such research, due to their distinctive properties
70 including large surface area and high electrochemical conductivity.^{37, 38} Several groups have
71 studied the nanocomposite of graphene-metal nanoparticles for electrochemical sensors for
72 detection of mycotoxins. Srivastava and co-workers have fabricated nickel nanoparticles
73 (NiNPs) on rGO for the detection of aflatoxin B (AFB₁).³⁹ Shukla and co-worker have
74 synthesized a reduced graphene oxide/tin oxide (rGO/SnO₂) nanocomposite for the detection
75 of patulin in apple juice.⁴⁰ Jiang and co-workers reported a synthesis of gold nanoparticles and
76 reduced graphene oxide (AuNPs-rGO) nanocomposite for the detection of OTA in wine
77 samples.⁴¹ However, the current literature review has not reported an aptamer-BSA
78 combination fabricated with AgNPs on rGO for the detection of OTA. It was observed that
79 there are no reports for the biosynthesis of AgNPs using amadumbe (*Colocasia esculenta*), a
80 staple diet in the African continent, mainly South Africa, Nigeria and Kenya.⁴² Thus, in this
81 study, a bioinspired AgNP-based probe able to detect OTA using Amadumbe extract will be
82 developed that is highly sensitive, cost-effective, and eco-friendly.

83 In the current study, a nanocomposite comprising of rGO/AgNPs as an electrochemical sensing
84 material was used in conjunction with an aptamer-BSA complex for the design of a rapid and
85 efficient OTA aptasensor. The signal amplification approach was achieved by anchoring the
86 aptamer onto the surface of rGO/AgNPs and making use of the interaction effect of rGO and
87 AgNPs fabricated onto carbon screen printed electrodes (C-SPEs). The C-
88 SPE/rGO/AgNPs/Apt/BSA exhibited good electrocatalytic detection for OTA in food samples.

89 Motivated by the previous work done prompted a combined quantum mechanical and Monte
90 Carlo simulations implemented to support the experimental methodology. Accordingly, the

91 electronic properties of the OTA in gas phase were investigated, using *ab initio* calculations
92 based on density functional theory (DFT). An analysis of the adsorption phenomena of these
93 electrode modifications has been carried out based on Monte Carlo simulations, which have
94 helped to improve our understanding of important surface phenomena that cannot be
95 determined just by experimentation.

96 To the best of our knowledge, the computational methodologies were performed in this study
97 for the first time to assess the electronic and structural properties between the OTA and the
98 BSA/Aptamer-nanocomposite. New insights into the interactions of OTA with the
99 nanocomposite can help as a general regulatory guideline for sensing applications in the food
100 industry.

101

102 **2. Experimental section**

103 **2.1 Chemicals and reagents**

104 The aptamer sequence 5'-GATCGGGTGTGGGTGGCGTAAAGGGAGCATCGGACA-3',
105 5'-thionine⁴³ was purchased from WhiteSci, Whitehead Scientific (Pty) Ltd (Durban, SA).
106 Amadumbe (*Colocasia esculenta*) and Weet-Bix purchased from a Durban supermarket.
107 Standards of OTA, (1 mg/mL in dimethyl sulfoxide) and aflatoxin B₁ (AFB₁), 3.79 µg/g in
108 acetonitrile were purchased from Sigma-Aldrich, Montpellier, France. Graphite powder, No.1
109 Whatmann filter paper, silver nitrate (AgNO₃), bovine serum albumin (BSA), chitosan (CS),
110 potassium permanganate (KMnO₄), potassium ferricyanide [Fe(CN)₆]³⁻, potassium
111 ferrocyanide [Fe(CN)₆]⁴⁻, sodium nitrate (NaNO₃, monosodium phosphate (NaH₂PO₄) and
112 disodium phosphate (Na₂HPO₄) were purchased from Sigma-Aldrich, Durban, SA. Sulphuric
113 acid (H₂SO₄) (97%, v/v), hydrogen peroxide (H₂O₂) (30%, w/w), hydrochloric acid (HCl)
114 (37%, v/v) were purchased from Laboratory Supplies, Durban, SA.

115

116 **2.2 Instrumentation**

117 All UV-vis spectrophotometric measurements were performed with VARIAN Cary 50
118 spectrophotometer (South Africa) in the wavelength ranging 200 to 800 nm. *Colocasia*
119 *esculenta* extract's functional groups and its role in the formation of nanoparticles were

120 analyzed using an attenuated total reflectance (Cary 630 FTIR Spectrometer from Agilent
121 Technologies, SA) spectra from 200 to 4000 cm^{-1} . The particle size analysis of the
122 biosynthesised AgNPs was performed using Single-particle ICP-MS (PerkinElmer NexION
123 2000 ICP-MS, Shelton, USA) equipped with the Syngistix nano software. The Asymmetric
124 Flow Field Flow Fractionation (AF2000) equipped with MALS and UV-vis detectors from
125 Postnova Analytics, Germany equipped with the AF2000 software was used for the separation
126 and the hydrodynamic size distribution of the biosynthesized nanoparticles. The morphological
127 characterization was carried with the high-resolution transmission electron microscopy (HR-
128 TEM) using a JEOL ARM 200F high-resolution transmission electron microscope (200 kV)
129 with an EDX analyzer (JED2300, at least 30 accumulations, matrix 512×512 points in STEM
130 mode- X-Max, Oxford Instruments, Germany).

131 The electrochemical measurements were performed at room temperature with a portable
132 combined bipotentiostat and spectrometer SPELEC Vis-NIR instrument from Metrohm SA.
133 The three-electrode configuration comprised of a working electrode (WE), a counter electrode
134 (CE) and a reference electrode (RE). The ProLab oven was used for drying purposes. A 781
135 pH/Ion meter from Metrohm SA was used for all the pH optimization measurements.

136

137 **2.3 Synthesis of Graphene Oxide (GO) and Reduced Graphene Oxide (rGO)**

138 In this work, GO was synthesized from natural graphite by slight modification of the
139 Hummers' method.^{44, 45} Approximately 1.2 g of graphite powder was oxidised by mixing with
140 2.0 g of NaNO_3 in 50 mL of concentrated H_2SO_4 . The reaction mixture was stirred in an ice
141 bath for 2 h, at a temperature range of 0-6 $^\circ\text{C}$, and thereafter 6.0 g of KMnO_4 was gently added
142 to the reaction mixture while stirring for another 2 h. Then it was removed from the ice bath
143 and heated to 30 $^\circ\text{C}$ while stirring for a further 2 h during which the reaction mixture changed
144 from black into a brownish paste. Then 8% of H_2O_2 was added into the reaction to weaken the
145 paste. At this stage, the colour of the solution changed from brown to golden yellow,
146 confirming the formation of GO. The resulting mixture was then centrifuged and washed 4
147 times with 8% HCl and deionized water respectively. Thereafter the filtrate was oven-dried
148 and crushed into a fine powder. The reduced form of graphene oxide (rGO) was obtained by
149 using chitosan as a reducing agent in the existing method. The conversion of GO to rGO was
150 achieved with a 10 x dilution with chitosan (10.0 mg/mL in 1.0% acetic acid) under vigorous

151 stirring for 9 h at 90 °C.⁴⁶ The resulting product was then oven-dried at 40 °C for 48 h in order
152 to obtain a powdered rGO.

153

154 **2.4 Synthesis of Silver Nanoparticles (AgNPs)**

155 The biogenic synthesis of AgNPs was conducted according to a previously reported method.⁴⁷
156 Fresh samples of amadumbe (*Colocasia esculenta*) as shown in **Figure S1B** were thoroughly
157 washed with tap water, followed with deionised water, and cut into smaller pieces. To obtain
158 the aqueous extract, 5.0 g of amadumbe pieces were boiled in 100 mL deionised water at 80
159 °C for 40 min and allowed to cool at room temperature. After cooling it was filtered through
160 No.1 Whatmann filter paper. Different parameters such as boiling temperature of the extract,
161 boiling time and the extracts amount were optimized for the complete reduction of silver. The
162 filtrate was then used as the reducing agent for the synthesis of AgNPs by adding approximately
163 4.0 mL of 1.0 mM aqueous AgNO₃. The mixture was then stirred at 150 rpm for 30 min at 80
164 °C.

165

166 **2.5 Preparation of rGO/AgNPs nanocomposite**

167 The rGO/AgNPs nanocomposite was prepared by mixing 0.5 mg/mL of rGO and AgNPs in a
168 ratio of 1:3 (v/v) in 50 mL of deionised water. The mixture was sonicated for 48 h to obtain a
169 homogenized paste.

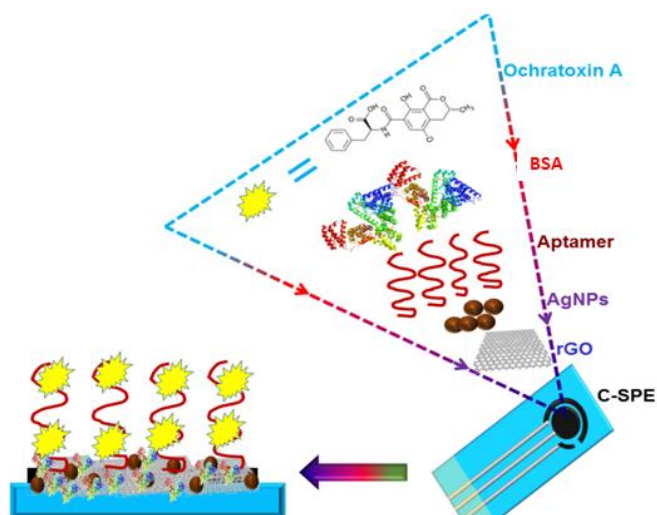
170

171 **2.6 Fabrication of C-SPE/rGO/AgNPs/Apt/BSA aptasensor**

172 The C-SPEs were first activated by applying a constant current of 3 μA for 2 min in 0.1 M
173 H₂SO₄ solution rinsed thoroughly with MilliQ-water, and 0.1 M phosphate buffer at pH 7.0.⁴⁸
174 The activated C-SPE was coated by casting 10.0 μL of rGO/AgNPs paste and dried at 37 °C
175 for 1 h. Thereafter 10.0 μL of 3.0 μM aptamer was dropped casted onto the rGO/AgNPs and
176 dried at 24 °C, followed by washing with phosphate buffer to remove the excess (unabsorbed)
177 aptamer from the C-SPE/rGO/AgNPs/Apt surface. Finally, the electrode was incubated with
178 1% (v/v) BSA solution for 20 min to completely block the unbound sites of the C-

179 SPE/rGO/AgNPs/Apt surface. The resultant OTA aptasensor electrode comprised of C-
180 SPE/rGO/AgNPs/Apt/BSA (**Scheme 1**).

181



182

183 **Scheme 1.** Design of the electrochemical OTA aptasensor C-SPE/rGO/AgNPs/Apt/BSA.

184

185 **2.7 Sample preparation**

186 The non-contaminated Weet-Bix sample was prepared by following the procedure reported by
187 He and co-workers.⁴⁹ An accurately weighed 4.0 g of the finely grounded sample was mixed
188 with 10 mL methanol-PBS (60:40, v/v) and allowed to stand for 5 min under ambient
189 conditions. The mixture was separated by filtration and the resulting methanol filtrate was
190 spiked with different concentrations of OTA.

191

192 **2.8 Characterization techniques**

193 **2.8.1 AF4-MALS**

194 The biosynthesised nanoparticles were separated and characterized with an AF4-based system.
195 The AF4 fractionation conditions are summarized in **Table S1**. AF4-MALS calibration was
196 performed using polystyrene nanoparticle standard mixtures as described in a previous study.⁵⁰

197

198 **2.8.2 SpICP-MS**

199 Single particle ICP-MS analyses were performed, operating in Standard mode as described in
200 a previous study.⁵¹⁻⁵⁴

201

202 **2.8.3 TEM**

203 Morphology studies were undertaken by transmission electron microscopy (TEM) as described
204 in a previous study.⁵⁰

205

206 **2.9 Electrochemical measurements**

207 The CV and DPV measurements were carried out in a redox probe of 1 mM $[\text{Fe}(\text{CN})_6]^{3-/4-}$
208 containing 0.1 M PBS. All the electrochemical measurements were performed at room
209 temperature in the potential range from -0.5 to 0.5 V.

210

211 **3. Computational methodology**

212 **3.1 Density Functional theory (DFT) Calculations**

213 Gaussian 09⁵⁵ was used to perform density functional theory (DFT) calculations on the
214 geometrically optimized 3D structure of OTA (**Figure S1A**) using the 6-311+G basis sets.
215 Further confirmation of the global minimum of the optimized geometry was obtained by
216 calculating the frequency. An important parameter for defining chemical activity is the energy
217 difference between the highest occupied molecular orbital (HOMO) and the lowest
218 unoccupied molecular orbital (LUMO), with a smaller value denoting a stronger tendency to
219 donate electrons. To confirm that the molecule has the ability to accept electrons in the
220 LUMO, HOMO and LUMO plots have been computed.

221

222 **3.2 Construction of the nanomaterials**

223 A 3D model of the GO surface was constructed based on the MS software's standard structural
224 database and features pristine graphite structures. Graphene oxide (GO) and silver

225 nanoparticles (AgNPs) are modeled using the Material Studio (MS) software package
226 developed by BIOVIA.⁵⁶ For the AgNPs, a 3-D model is defined according to its standard
227 structural database within MS. In order to assess their feasibility, an energy minimization
228 procedure was conducted for each, followed by an optimization of geometry using a Forcite
229 module with an ultrafine-COMPASS force field.⁵⁷ In this study, the maximum values of
230 energy, force, stress, and displacement were set to be 2×10^{-5} kcal/mol, 0.001 kcal/mol, 0.001
231 GPa, and 10^{-5} Å respectively.

232

233 **3.3 Molecular construction of the aptamer sequence**

234 Based on the sequence, the secondary structure of ssDNA was built using M-fold, and refined
235 equivalent 3D ssRNA models were constructed using Chimera, translated to ssDNA models
236 by VMD.⁵⁸ The BSA (PDB code: 4F5S) structure was extracted from the protein database into
237 MS to predict the interaction with the aptamer sequences. Discovery Studio visualizer was then
238 used to explore the aptamer-BSA interaction. The selected aptasensor sequence was then
239 synthesised by the local supplier.

240

241 **3.4 Adsorption Studies by Monte Carlo Simulations**

242 The lowest energy configurations of adsorbates on some selected substrates have been
243 determined by Monte Carlo (MC) adsorption studies. By replicating the experimental layer-
244 by-layer electrodes, the substrates and adsorbates were constructed (**Scheme 1**). Adsorption
245 Locator (AL) functionality (MS software)⁵⁶ was used for each generated configuration, thereby
246 showing the best adsorption sites. Analogues of the electrochemical layer-by-layer strategy
247 were modelled by carrying out Monte Carlo simulations of the substrate–adsorbate
248 conformational space since the temperature slowly decreased in accordance with a simulated
249 annealing strategy during the adsorption process.^{56,59}

250 Among the resulting adsorbate-substrate structures, the lowest adsorption energy conformers
251 were each optimized for a stable conformation, and the adsorption energies are listed in **Table**
252 **2**.

253

254 4. Results and Discussion

255 4.1 Experimental section

256 4.1.1 Characterization of biosynthesized AgNPs

257 (i) AF4-MALS

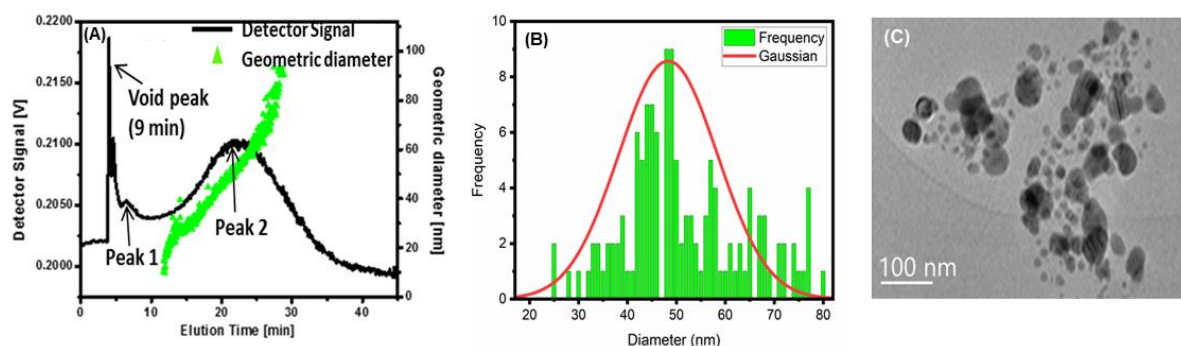
258 The fractogram in **Figure 1A** represents the particle size distribution of AgNPs by AF4-MALS,
259 under the optimised parameters indicating a clear separation from the void peak. The diameter
260 of the particles (D_{geo}) for the elution time ranging from 10 to 25 min, results in the average
261 geometric diameter of 55 nm.

262 (ii) spICP-MS

263 The spICP-MS was used to determine the size of the nanoparticles at low concentrations. The
264 internal calibration with an isotope dilution was used to determine the size of AgNPs. **Figure**
265 **1B** revealed a size-based diameter, $d = 48$ nm.

266 (iii) TEM

267 The size, shape and morphology of AgNPs were identified using transmission electron
268 microscopy (TEM). The TEM image (**Figure 1C**) confirms that the biosynthesized AgNPs are
269 spherically shaped, with the average particle size of 53 nm. Veisi and co-workers reported a
270 spherical shape of AgNPs, when they used plant extract as a reducing agent.⁶⁰ The TEM crystal
271 lattice image (**Figure S1C**) shows the spherical nature of the particles that are highly
272 crystallized; this is confirmed by the uniform lattice fringes. The lattice spacing of 0.23 nm
273 corresponds to (111) planes of silver.



274

275 **Figure 1.** (A) AF4-MALS fractogram; (B) spICP-MS and (C) TEM images for biosynthesised AgNPs.

276

277 **4.1.2 Spectroscopic characterization of rGO/AgNPs nanocomposite and C-** 278 **SPE/rGO/AgNPs/Apt/BSA**

279 **(i) UV-Vis spectra**

280 The reduction of Ag (I) to Ag (0) was observed by a colour change from colourless to brown
281 and it was monitored by UV-Visible (**Figure S1D**). **Figure 2A** shows the UV-Visible spectra
282 of (i) Amadumbe extract and (ii) AgNPs under the optimized conditions. The surface plasmon
283 resonance (SPR) absorption band at 428 nm is observed, which is lower than that obtained by
284 other researchers.^{61, 62} This shows that the synthesized AgNPs are spherical in shape, in
285 agreement with (TEM images in **Figure 1C**) and those reported by Alsharif et al (2020) and
286 Ndikau et al (2017).^{63, 64} The UV-Visible was also used for the characterization of GO and
287 rGO. A distinct absorption band for GO was observed at 238 nm with a shoulder absorption
288 band 298 nm (**Figure 2B**). These bands are associated with the $\pi \rightarrow \pi^*$ aromatic (C=C) and
289 $n \rightarrow \pi^*$ (C=O) transitions, respectively. Similar results were reported in literature.⁶⁵⁻⁶⁷ The
290 absorption band of rGO red shifted to 265 nm depicting an accumulation of electrons and the
291 removal of some functional groups on the GO surface.^{66, 68, 69} The removal of oxygen and the
292 C=O groups from GO results in the disappearance of the shoulder peak at 298 nm.⁶⁹

293

294 **(ii) ATR spectra**

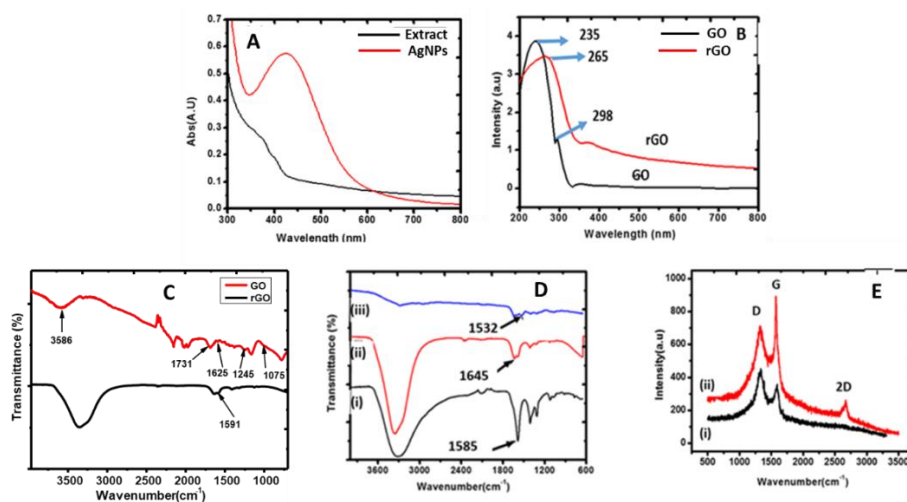
295 The ATR spectroscopy was used to identify the oxygen-containing functional groups that are
296 present in the synthesised carbonaceous material. The ATR spectrum of GO and rGO (**Figure**
297 **2C**) shows an intense peak at 3586 cm^{-1} , corresponding to the O–H groups of the adsorbed
298 water molecules between the GO sheets, demonstrating the hydrophilic characteristic of GO.
299 The C=O stretching, aromatic C=C vibrations, epoxy C-O stretching vibration and the alkoxy
300 C–O stretching vibrations were observed at 1731, 1625, 1245 and 1075 cm^{-1} respectively in the
301 GO spectrum.⁷⁰⁻⁷⁴ After the reduction of the GO, the peak at 1731 cm^{-1} disappeared, suggesting
302 the elimination of the oxygen-containing functional groups, such as C=O and C-O bonds.^{75, 76}
303 The intense peak at 1591 cm^{-1} indicates the restoration of the sp^2 carbon networks.⁷⁷ The
304 functional groups that are present in all fabrication steps of the aptasensor as shown in **Figure**
305 **2D**. The ATR spectra of C-SPE rGO/AgNPs shown in **Figure 2D (i)** is similar to that of rGO

306 but there is a weak intensity with a minor blue shift from 1585 to 1591 cm^{-1} , arising from the
 307 large presence of AgNPs.⁷⁸ After the immobilization of the aptamer onto the electrode surface,
 308 **Figure 2D (ii)**, the C=O peak at 1645 cm^{-1} was observed, this confirmed the formation of
 309 metal-DNA aptamer bonding on the electrode surface.⁷⁹ The incubation of the blocking agent,
 310 BSA, on the electrode surface resulted in the secondary amide peak at 1532 cm^{-1} , indeed
 311 confirming the adsorption.

312

313 (iii) Raman Spectra

314 The Raman spectroscopy was used to characterize rGO before and after AgNPs were absorbed
 315 on the surface as shown in **Figure 2E**. The graphite spectrum is characterized by the G and D-
 316 bands. These two main bands are attributed to the disorder in the C-C bonds and the in-plane
 317 vibration bonds respectively.⁸⁰ The 2 characteristic D and G bands around 1320 cm^{-1} and 1586
 318 cm^{-1} were observed on the rGO spectra before AgNPs modification (**Figure 2E (i)**). The D
 319 band provides information of the breathing mode of the k-point, while the G band relates to the
 320 tangential stretching mode of the E_{2g} phonon of the sp^2 carbon atoms.⁸¹ After the AgNPs were
 321 decorated onto the rGO, the intensity of D and G bands observed at 1327 cm^{-1} and 1574 cm^{-1}
 322 respectively were then enhanced (**Figure 2E (ii)**) because of the surface enhanced Raman
 323 scattering of nanoparticles.



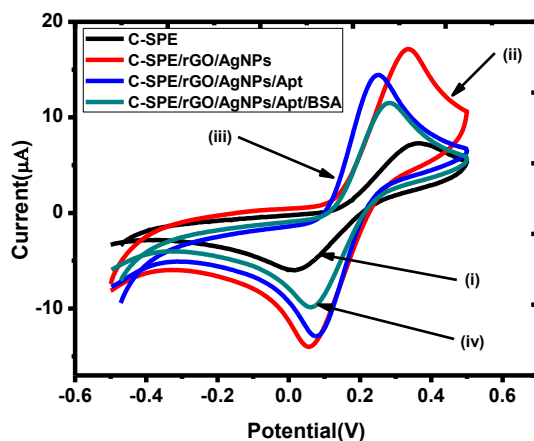
324

325 **Figure 2.** UV-Vis spectra of (A) AgNPs and Amadumbe extract, (B) GO and rGO; ATR spectra of (C) GO and
 326 rGO; and (D) (i) C-SPE/rGO/AgNPs, (ii) C-SPE/rGO/AgNPs/Apt, and (iii) C-SPE/rGO/AgNPs/Apt/BSA; and
 327 (E) Raman spectra of (i) rGO and (ii) rGO/AgNPs.

328

329 4.1.3 Electrochemical characterization of C-SPE/rGO/AgNPs/Apt/BSA

330 Cyclic voltammetry (CV) is one of the most useful techniques in the evaluation of the
331 electrochemical behaviour of modified electrodes. **Figure 3** shows the cyclic voltammograms
332 attained at the fabricated aptasensor in 5.0 mM $[\text{Fe}(\text{CN})_6]^{3-/4-}$ prepared in a 0.1 M PBS buffer
333 at pH 7. The bare C-SPEs displayed a well-defined redox peak which corresponds to the
334 reversible redox reaction of $[\text{Fe}(\text{CN})_6]^{3-/4-}$. After deposition of rGO/AgNPs composite, a
335 significant increase in the redox peak current was observed, due to the presence of improved
336 conductivity properties of rGO and AgNPs. The rGO/AgNPs composite promoted an electron
337 transfer because of the increased surface area. The oxygen groups in GO provided a selective
338 interface for the deposition of AgNPs. The π - π stacking interaction present in rGO accelerated
339 the electron transfer and AgNPs conductivity.⁸² After immobilization of the aptamer, a
340 decrease in the redox peak suggests that the presence of the aptamer on the electrode surface
341 hinders the electron transfer.⁸³ A further decrease in the peak current was observed on
342 immobilization of BSA due to the blocking of the non-specific binding sites of the aptasensor,
343 demonstrating a successful immobilization onto the electrode surface. The anodic peak
344 potential (E_{pa}) shifts towards the left, while the cathodic peak potential (E_{pc}) shifts towards the
345 right, this indicates an efficient mass transfer between the modified electrodes.⁸⁴



346

347 **Figure 3.** Comparative cyclic voltammograms of (i) bare C-SPE, (ii) C-SPE/rGO/AgNPs, (iii) C-
348 SPE/rGO/AgNPs/Apt and (iv) C-SPE/rGO/AgNPs/Apt/BSA in 1 mM $[\text{Fe}(\text{CN})_6]^{3-/4-}$ and 0.1 M PBS (pH 7.0) at
349 a scan rate of 20 mV/s and (B) dependence of the peak potential shift at different electrode types.

350

351 4.1.4 Optimization of experimental conditions

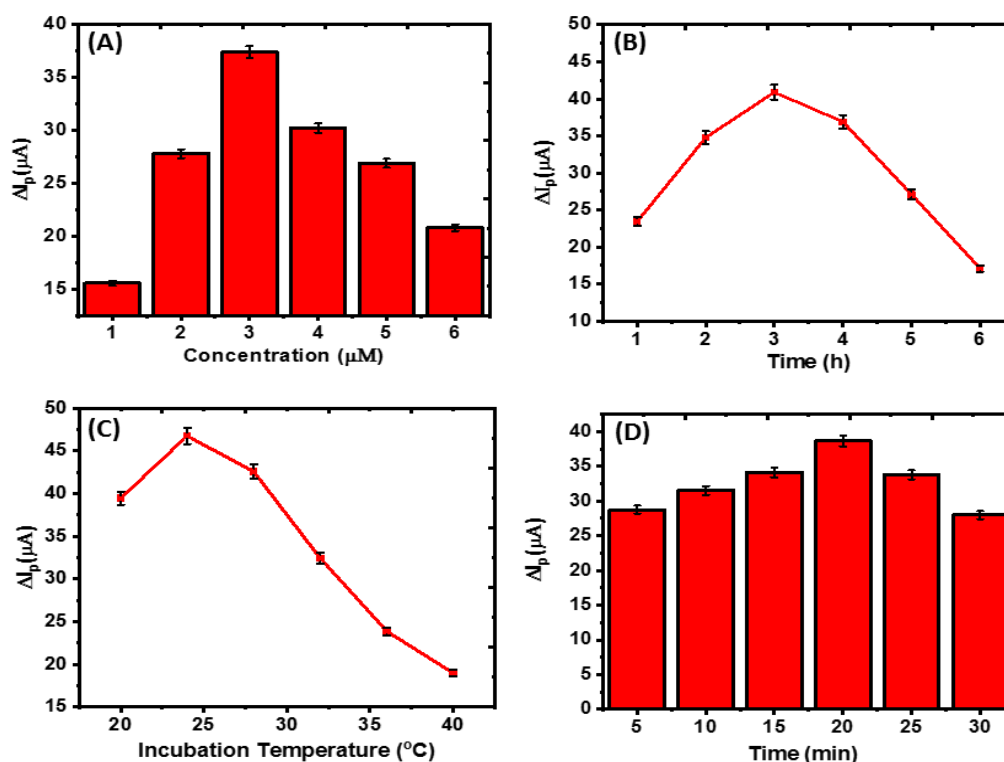
352 In order to attain an outstanding analytical performance of the proposed aptasensor, the ratio,
353 aptamer concentration, incubation time, incubation temperature, the OTA incubation time, and
354 pH were optimized. The peak currents gradually increase with increasing rGO: AgNPs ratios
355 (**Figure S2A**), because of the deposition of more metallic AgNPs with good electroactivity
356 onto the modified electrode. The optimum value of the peak currents were observed at a ratio
357 of 1:3, beyond which it decreases due to the reduction of the electron transfer efficiency. This
358 is a significant result as it also limits the amount of aptamer immobilized onto the C-
359 SPE/rGO/AgNPs surface.

360 The effect of the aptamer concentration was studied by modifying the electrode with
361 concentrations ranging from 1 to 6 μM as shown on **Figure 4A**. The current response increases
362 from 1 to 3 μM with a maximum of 37.5 μA , and thereafter decreases because of a poor
363 interfacial electron transfer of the aptamer. The incubation time of the 3 μM aptamer was
364 optimized by monitoring the current responses for 6 h (**Figure 4B**). There is an increase in
365 current with increasing incubation time reaching a maximum of ΔI_{pa} at 3 h, beyond which it
366 decreases due to a longer incubation time, resulting in the partial hybridization of the aptamer.
367 Consequently, 3 h was selected as the optimum incubation time.

368 DNA has a specified working temperature due to the presence of different functional groups
369 that may affect the incubation temperature when fabricating the aptasensor. **Figure 4C** shows
370 an increase in ΔI_{pa} results in an increase of the incubation temperature up to 24 $^{\circ}\text{C}$ and thereafter
371 it gradually decreases. Peng and co-workers revealed that the high incubation temperature
372 decomposes the aptamer.⁸⁵ Therefore 24 $^{\circ}\text{C}$ of the incubation time was used for the entire
373 experiment. This demonstrates the optimum performance of the DNA at room temperature, in
374 accordance with the accompanying safety sheet provided by supplier, Whitehead Scientific
375 (Pty). The analytical performance of the aptasensor on the recognition time of aptamer to OTA
376 was also evaluated as shown in **Figure 4D**. The current response increased with an increasing
377 of the incubation time from 5 to 20 min. When the incubation time was more than 20 min, the
378 current response decreases, suggesting that the bio-recognition reaction was completed. Hence,
379 20 min of incubation time was chosen. pH value is another significant factor that affects the
380 response of the sensor. Su and co-workers previously reported that an acidic and basic
381 environment could damage the negatively-charged aptamer and therefore affects the interaction

382 between the aptamer and their targets.⁸⁶ The effect of pH on the current response of the C-
 383 SPE/rGO/AgNPs/Apt/BSA towards OTA was evaluated at pH 4 to 8 (**Figure S2B**). The current
 384 response towards OTA increases until it reaches pH 7 and then it decreases. This result
 385 confirms that the aptasensor performance is pH dependent; hence all the electrochemical
 386 measurements were conducted at pH 7 to ensure that the fabricated aptasensor functions at its
 387 maximum sensitivity.

388



389

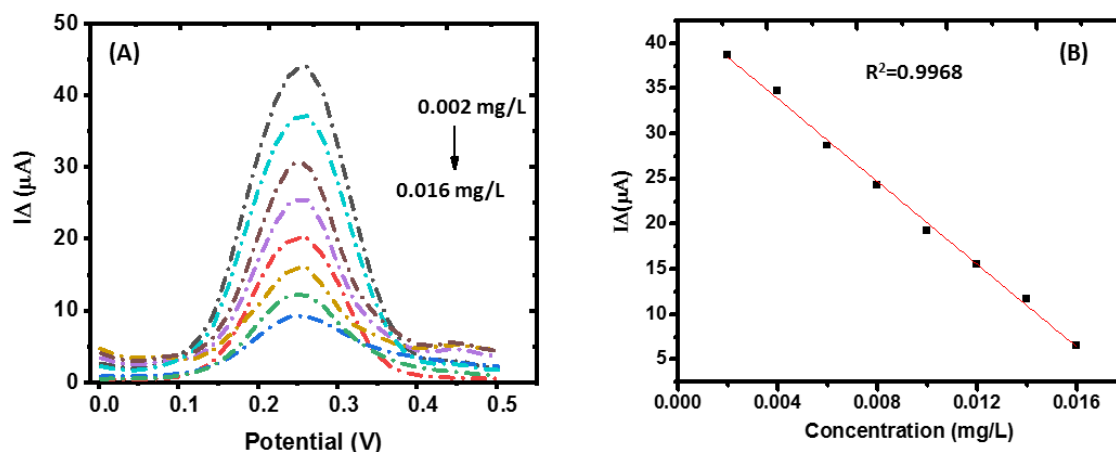
390 **Figure 4.** Effect of the aptamer (A) concentration, (B) incubation time, (C) incubation temperature; and (D) Effect
 391 of OTA incubation time.

392

393 4.1.5 Analytical performance of the fabricated aptasensor

394 The analytical performance of the fabricated aptasensor was examined by assessing the DPV
 395 current response of the aptasensor incubated with OTA concentrations ranging from 0.002 to
 396 0.016 mg/L. **Figure 5A** shows a linearly decreasing peak current with an increasing OTA
 397 concentration. This shows that the aptamer was folded and the formation of OTA-Apt
 398 complexes on the sensing interface causes inhibition of electron transfer of the redox probe

399 $[\text{Fe}(\text{CN})_6]^{3-/4-}$. Quantitative detection of OTA was then carried out by observing the decrease
400 of DPV responses of $[\text{Fe}(\text{CN})_6]^{3-/4-}$ peak current by increasing OTA concentration. Under the
401 optimal conditions, the calibration curve of the fabricated aptasensor yielded a linear range
402 from 0.002 to 0.016 mg/L with a correlation coefficient of 0.9968 (**Figure 5B**). The LOD was
403 7×10^{-4} mg/L, and with a similar linear dynamic range observed in previous studies (**Table 1**).
404



405
406 **Figure 5.** (A) The DPV response of C-SPE/rGO/AgNPs/Apt/BSA in 1 mM $[\text{Fe}(\text{CN})_6]^{3-/4-}$ after incubation with
407 different concentrations of OTA from (0.002-0.016 mg/L); and (B) The linear calibration curve of (ΔI_p) with OTA
408 concentrations.

409

410 **Table 1. Comparison of the various reported biosensors for the detection of OTA**

411

Strategy	Sensing Technique	Linear range	LOD	Stability (days)	Reference
Apt/SWCNHs	Fluorescence	20–50 Nm	17.2 nM	-	87
dsDNA/PG	Fluorescence	1–1×10 ⁵ ng/mL	1.0 ng/mL	-	88
G-quadruplex-ThT/FRET	FRET	5–700 ng/mL	0.4 ng/mL	-	89
GCE/CdTe/CS/cDNA/BSA/Cy	(ECL-RET)	5×10 ⁻⁴ –50 ng/mL	0.2 pg/mL	5	90
5-pDNA	Fluorescent	5–200 ng/mL	1.3 ng/mL	10	91
Th–Au octahedral–dsDNA/SA–GR/GCE	Electrochemical	0.001–5 ng/mL	0.1 pg mL	14	92
BSA/Apt/AgNP s-rGO/C-SPE	Electrochemical	0.002–0.016 mg/L	7 ×10 ⁻⁴ mg/L	20	This work

412 Single-walled carbon nanohorns (SWCNHs), aptamer (Apt), double strand (ds) Deoxyribonucleic acid (DNA),
 413 Pico Green (PG), fluorescence resonance energy transfer (FRET), electrochemiluminescence resonance energy
 414 transfer (ECL-RET), glassy carbon electrode (GCE), Cadmium telluride (CdTe), chitosan (CS), capture DNA
 415 (cDNA), cyanine dye (Cy5), probe DNA (pDNA), Bovine serum albumin (BSA), silver nanoparticles (AgNPs),
 416 reduced graphene oxide (rGO), carbon screen printed electrode (C-SPE)

417

418 4.1.6 Specificity, reproducibility and stability of designed aptasensor

419 To evaluate the specificity of the proposed aptasensor in response to OTA in the presence of
 420 AFB₁, the fabricated aptasensor was incubated in a mixture of 0.002 mg/L and 0.01 mg/L of
 421 OTA and AFB₁ respectively. **Figure S3A** shows a major current response when the aptasensor
 422 was incubated with 0.002 mg/L of OTA and the mixture, while the incubation of 0.01 mg/L
 423 AFB₁ showed a negligible DPV signal, indicating that the fabricated aptasensor is highly
 424 specific towards OTA.

425 The reproducibility of the fabricated aptasensor was studied by the incubation of 0.002 mg/L
426 OTA in six independent aptasensors. The six measurements with a relative standard deviation
427 (RSD) of 3.5% (**Figure S3B**), demonstrating a good reproducibility of the fabricated
428 aptasensor.

429 In addition, the stability of the aptasensor was evaluated for 20 days. Measurements were
430 recorded at 5-day intervals with an initial current response which decreased to 87.8% (**Figure**
431 **S3C**), signifying an acceptable stability of the developed aptasensor. The aptasensor was stored
432 in a refrigerator at 4 °C when not in use.

433

434 **4.1.7 Analytical application of aptasensor**

435 The proposed aptasensor was used for the detection of OTA in Weet-Bix samples. Three OTA
436 standards were added into the extracted samples, with the recoveries ranging from 94.00 to
437 106.25% (**Table S1**). These results indicate the reliability and the prospective applicability of
438 the proposed aptasensor in food security monitoring.

439

440 **4.2 Computational Section**

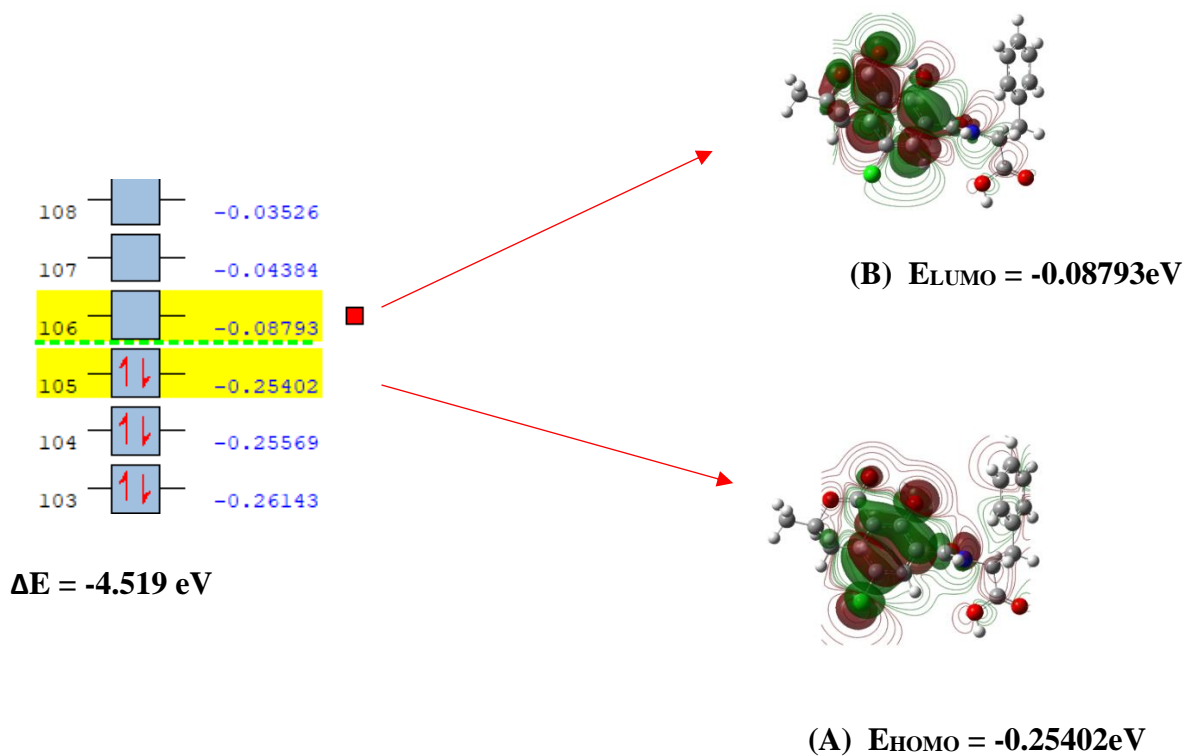
441 In this work, computational modelling was undertaken to better understand the electron transfer
442 capabilities of OTA, computed at the density functional theory (DFT) level as discussed below.

443

444 **4.2.1 HOMO-LUMO DFT Calculations**

445 **Figure 6A-B** illustrates the HOMO-LUMO plots obtained at the DFT level of theory.
446 Molecular orbitals with the highest energy are considered to be the highest occupied (HOMO)
447 and have the ability to donate electrons. This lower unoccupied molecular orbital (LUMO)
448 informs us that this orbital has an empty electron space, thus suggesting the possibility of
449 acquiring the donated electrons.⁹³ The calculated energy gap of -4.519 eV supports this greater
450 tendency to donate electrons.

451



452 **Figure 6.** The plots for (A) HOMO, (B) LUMO.

453

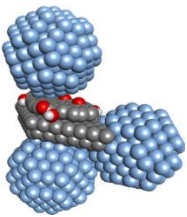
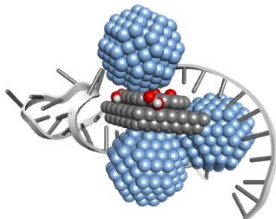

454 In **Figure 6A**, the electrons located in the highest occupied molecular orbitals (HOMO) orbit
 455 around the oxygen atoms in chlorophenolic groups containing dihydro-isocoumarin rings. In
 456 accordance with their location, the lowest unoccupied molecular orbitals (LUMO) on
 457 chlorophenolic rings have dihydro-isocoumarin rings (**Figure 6B**). According to the results
 458 obtained above, carbonyl groups in esters will be a convenient way for electrons to be added
 459 to the molecule.

460

461 **4.2.1 Monte Carlo Adsorption Studies**

462 In this section, we used Monte Carlo simulation methods to calculate the adsorption energies
 463 of amorphous adsorbates and substrates to mimic the experimental electrochemical layers
 464 (**Scheme 1**). The adsorption energies for the geometry optimized structures are shown in **Table**
 465 **2** along with an additional energy decomposition based on the adsorption locator algorithm
 466 (**Table S2**).

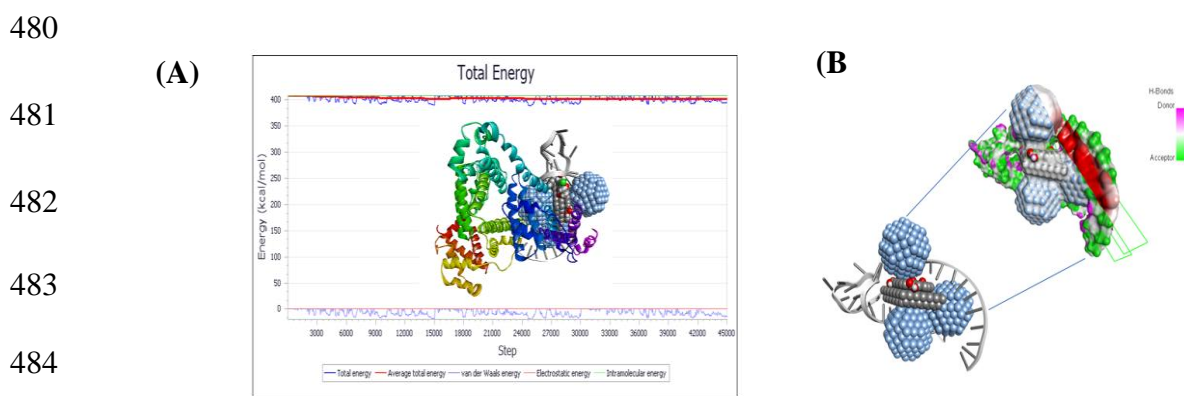
467 **Table 2. The adsorption energy distributions C-SPE/rGO/AgNPs/Apt/BSA**

Substrate	Adsorbate	optimized 3-D structure	adsorption energy kcal/mol
C-SPE/rGO	AgNPs	 <p data-bbox="815 613 1007 640">C-SPE/rGO/AgNPs</p>	-3.1764 x 10³
C-SPE/rGO/AgNPs	Apt	 <p data-bbox="815 972 1050 999">C-SPE/rGO/AgNPs/Apt</p>	-1.0637 x 10³
C-SPE/rGO/AgNPs/Apt/	BSA	 <p data-bbox="815 1339 1102 1366">C-SPE/rGO/AgNPs/Apt/BSA</p>	-198.222

468

469

470 Calculated negative adsorption energies indicate stabilization and an exothermic adsorption
 471 process.^{94, 95} The lower the negative energy, the stronger the adsorption between the adsorbate
 472 and substrate. Based on the increase in the anodic peak current observed at $E_{pa} = + 0.3V$ in
 473 **Figure 3** (ii) of our nanocomposite, the presence of the aptamer greatly contributes to its
 474 stabilization. However, the adsorption energy decreased significantly after BSA was
 475 immobilized, as confirmed by a reduction in the peak current (**Figure 3** (iv)), due to the
 476 blocking of the non-specific binding sites of the aptasensor. **Figure 7A** demonstrates the
 477 presence of an effective bio-molecular interaction between OTA and the aptamer complex, as
 478 it correlates well with the experimental results. A hydrogen bonded interaction between an
 479 aptamer and a rGO/AgNPs nanocomposite is shown in **Figure 7B**.



485

486 **Figure 7.** (A) Total energy decomposition plots and 3D representation for SPE/rGO/AgNPs/Apt/BSA-OTA; and
 487 (B) the corresponding 3D hydrogen bonded interaction plots for SPE/rGO/AgNPs/Apt.

488

489 5. Comparison of experimental data with computational results

490 The CV for the layer-by-layer electrode fabrication process (**Figure 3** (ii-iv)) demonstrates a
 491 linearly decreasing anodic peak current according to the following trend: (ii) C-
 492 SPE/rGO/AgNPs > (iii) C-SPE/rGO/AgNPs/Apt > (iv) C-SPE/rGO/AgNPs/Apt/BSA. The
 493 corresponding modelled structures obtained from Monte Carlo simulations resulted in an
 494 increase in adsorption energy (**Table 2**). This means that the presence of AgNPs fabricated
 495 onto C-SPE/rGO nanocomposite is most strongly bound and is attributed to the highly negative
 496 adsorption energy (-3.1764×10^3 kcal/mol) between the adsorbate-substrate system. Our
 497 simulation results indicate that the highly stabilized (C-SPE/rGO/AgNPs) layer is attributed to

498 the presence of the high energy rGO-AgNPs nanocomposite (**Table S2**), in agreement with the
499 amplified electrochemical signals depicted in **Figure 3** (ii). On the other hand, the presence of
500 the aptamer greatly contributes to a lowering of the peak current (**Figure 3** (iii)) with a
501 corresponding increase in the adsorption energy for the nanocomposite C-
502 SPE/rGO/AgNPs/Apt. Finally, the adsorption energy increased significantly after the
503 immobilization of BSA, with a further decrease in the peak current observed in **Figure 3** (iv).
504 This is attributed to blocking of the non-specific binding sites of the aptasensor as illustrated
505 in **Figure 7A-B**. Clearly, the highly negative adsorption energy observed when OTA interacted
506 with the C-SPE/rGO/AgNPs/Apt/BSA, demonstrates the existence of a good bio-molecular
507 interaction between OTA and the aptamer complex which correlates well with the experimental
508 results.

509

510 **6. Conclusions**

511 The purpose of this study was to develop an electrochemical aptasensor capable of
512 detecting OTA in commercial Weet-Bix samples with high sensitivity and efficiency. With a
513 combination of experimental and computational techniques, we demonstrated that the
514 nanocomposite construction utilizing rGO and AgNP and OTA detector provided good
515 sensitivity, were easy to use, and were cost effective. Further, all the techniques utilized in this
516 study allowed simultaneous morphological and size analyses. It can be concluded that AF4-
517 MALS, spICP-MS, and TEM analyses are accurately inferring the presence of nanoparticles.
518 According to AF4-MALS analysis, the geometric diameter of AgNPs was 55 nm, while the
519 mean particle size distribution diameter was 48 nm, and the core size was 53 nm in TEM
520 analysis. Furthermore, the images obtained by TEM confirmed that the synthesized AgNPs
521 were spherical in shape. Using the proposed aptasensor, the concentration range was enhanced
522 from 0.002 to 0.016 mg/L with an LOD of 7×10^{-4} mg/L. Moreover, the presence of AFB₁ did
523 not show any significant changes in the current. Ample evidence of the effectiveness of the
524 proposed aptasensor system was obtained when Weet-Bix samples were spiked. A good
525 recovery was obtained with an acceptable range (94.00 to 106.25%).

526

527 The use of computational modeling has also provided structural information about
528 interactions between biomolecules and nanostructures, as well as electronic properties of OTA.
529 Electrochemically modified aptasensors show good agreement with computed adsorption
530 energies and current responses. Weet-Bix samples can be detected by the proposed aptasensor
531 using disposable C-SPEs on-site using the disposable C-SPEs.

532

533 **Conflict of interest**

534 The authors declare that there is no conflict of interest regarding the publication of this
535 manuscript.

536

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541

542 **Supporting Information**

543 Graphical representation of OTA, amadumbe image, HR-TEM image for AgNPs, reduction of
544 AgNPs, graphical representation of the rGO: AgNPs, representation of pH on change in peak
545 currents, graphical representation of specificity of the aptasensor in AFB₁, representation of
546 reproducibility of the aptasensor with independent electrodes, representation of the storage
547 stability of the OTA aptasensor, tabulated recoveries of OTA, tabulated energy decomposition.

548

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