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## Electrochemical strategies for gallic acid detection: Potential for application in clinical, food or environmental analyses

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1 **Electrochemical strategies for gallic acid detection: Potential for application in clinical,**  
2 **food or environmental analyses**

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28

29 **Abstract**

30 Polyphenols are important to human health thus making it interesting and necessary to  
31 identify and assess methods for their detection. Gallic acid (GA) is a well-known antioxidant  
32 compound, found in tea leaves, various fruits, fruit seeds and in fruit-derived foods and  
33 beverages. In this study, to electrochemically detect this compound and assess the potential  
34 for GA detection, different analytical conditions at pH values of 5.8, 7 and 8 were tried. Two  
35 types of device were used for GA detection: (1) Lazar ORP-146C reduction-oxidation  
36 microsensors, coupled with a Jenco device, for estimation of antioxidant capacities of  
37 different electroactive media, and (2) screen-printed carbon sensors coupled with a mobile  
38 PalmSens device using differential pulse voltammetry (qualitative and quantitative GA  
39 determination). These proposed methods were validated by analysing some real samples:  
40 wine, green tea, apple juice and serum fortified with GA. Detection was evaluated in terms  
41 of specific calibration curves, with low limit of detection (LOD) and limit of quantification  
42 (LOQ), low response time, and high sensitivities. The analytical characteristics obtained  
43 recommend these methods to be tested on more other types of real samples. Our proposed  
44 methods, used in the established conditions of pH, may have further application in other  
45 clinical, food or environmental samples analyses in which the results of total antioxidants  
46 contents are usually expressed in GA equivalents.

47

48 **Keywords:** electrochemical detection; gallic acid; differential pulse voltammetry;  
49 screen-printed carbon electrode; redox microsensor

50

## 51 **1. Introduction**

52 Polyphenols are universally present in plant-derived foods and their effects on human  
53 health have been extensively studied over the past twenty years. Their metabolites have been  
54 associated with the health benefits of plant-derived foods (Abdel-Daim et al., 2018; Bispo et  
55 al., 2017). The use of natural products in discovering and developing anticancer drugs is  
56 frequent, with over 50% of medicinal products used in antitumor clinical trials being isolated  
57 from natural sources (Tietbohol et al., 2017).

58 Among these natural products, plant-derived compounds are important sources of  
59 multiple anticancer clinical agents, plants being well known as sources of molecules with  
60 pharmacological activity (Pellegrina et al., 2005). Some studied compounds, such as gallic  
61 acid (3,4,5-trihydroxybenzoic acid, GA) and its derivatives have been extensively evaluated  
62 for their antitumor activity against various cell lines (Petrea, et al., 2018; Sourani et al.,  
63 2016).

64 GA has been identified as having various biological activities. Antibacterial (Dos Santos  
65 et al., 2018), antiviral (You et al., 2018), anti-inflammatory, antihistaminic and antitumor  
66 activities, scavenging of free radicals and protection against cardiovascular diseases (Mudnic  
67 et al., 2010; Seob et al., 2018), antioxidant (Asnaashari et al., 2014; Suwalsky et al., 2016;  
68 Hsu et al., 2016), anticancer (Wang et al., 2014; Locatelli et al., 2013; Verma et al., 2013),  
69 antidiabetic (Kong et al., 2018; Huang et al., 2016), etc., have all been reported. Studies have  
70 shown that GA can inhibit the mitochondrial dysfunction with a significant neuroprotective  
71 effect on cerebral ischemia/reperfusion injury (Sun et al., 2017). The beneficial effects of GA  
72 derivatives (methyl, propyl, octyl and dodecyl gallate) are also known for their widespread  
73 use as antioxidants in the pharmaceutical and cosmetic industries (Nayeem et al., 2016;  
74 Otrisal et al., 2017).

75 GA is one of the main natural phenolic acids existing in tea leaves (both green and black  
76 tea), grapes (grape seeds), fruits such as strawberries, berries and other fruits, as well as in  
77 many other processed herbs and drinks – red tea and red wine (Suwalsky et al., 2016; Hsu et  
78 al., 2016). Detection of GA is often considered as an indicator of the authenticity of fruit  
79 juices and different alcoholic beverages, and in recent years it has been illegally added to

80 liquors (Ng et al., 2000). GA is also found in several hardwood species such as oak (oak bark)  
81 and chestnut; also, it can be obtained under acid hydrolysis of hydrolysable tannins (Liu et  
82 al., 2016; Prikryl et al., 2018; Zhang et al., 2014). Consequently, quantitative determination  
83 of GA concentration can be made for food, medicinal plants and, last but not least, in body  
84 fluids (Shahrzad and Bitsch, 1998). GA usually indicates the total level of antioxidants (total  
85 antioxidant capacity) of the real samples and the results are expressed as Gallic Acid  
86 Equivalents (GAE) (Xiong et al., 2017).

87 Thus, we can underline the importance of identifying different viable alternatives to  
88 detect GA from different matrices. In recent years, different detection methods have been  
89 developed and optimized to detect GA in different samples using thin-layer (Dhalwal et al.,  
90 2008) or liquid chromatography (Shahrzad and Bitsch, 1998; Narumi et al., 2014; Denderz  
91 and Lehotay, 2014; Keckes et al., 2013). The antioxidant activity (AOA) of wine samples  
92 has been evaluated spectrophotometrically, as a measure of radical scavenging activity, using  
93 a 1,1-diphenyl-2-picryl-hydrazyl free radical molecule (DPPH) (Brand-Williams et al., 1995;  
94 Leong and Shui, 2002; Di Lorenzo et al., 2017). A  
95 2,2-azinobis-(3-ethylbenzothiazoline-6-sulfonate (ABTS) assay with some modifications  
96 was performed (Re et al., 1999).

97 Electrochemical and kinetic methods are highly useful for detection and monitoring of  
98 electroactive chemical/biochemical species (Bungau et al., 2017; Bungau et al., 2012; Badea  
99 and Badea, 2006; Supalkova et al., 2006; Tukimin et al., 2017; Radovici et al., 2003). Some  
100 of the biotechniques used are based on receptor-receptor interaction (Eremia et al., 2013;  
101 Garcia et al., 2015).

102 We performed an intensive and systematic review of the existing research about GA  
103 detection using electrochemical methods with carbon-based electrodes. Moreover, it was  
104 possible to identify the gaps in this area and to underline the additional value of the present  
105 study. The trend of the identified articles showed an increased interest in GA only after 2000.  
106 Some papers referred to biosensors using laccase (Vlamidist al., 2017) and tyrosinase (Datta  
107 et al., 2017) as analytical tools for GA detection and other plant-derived antioxidants. GA  
108 was also mentioned as a reagent used to modify different carbon electrodes (multi-walled

109 carbon nanotubes and electropolymerized GA (poly(gallic acid)/MWNT/GCE) (Ziyatdinova  
110 et al., 2018) to detect other bioactive compounds.

111 With the advantages of electroanalytical methods (Petkovic et al., 2015; Sangeetha and  
112 Narayanan, 2014; Jara-Ulloa et al., 2013; Tashkhourian et al., 2013; Liang et al., 2016;  
113 Tashkhourian and Nami-Ana, 2015; Raymundo-Pereira et al., 2015; Šcorc et al., 2018),  
114 different studies have been conducted to determine GA, using different designs of transducer  
115 systems.

116 Analysing the scientific literature, we found articles dealing with detection of GA or  
117 with determination of its antioxidant action by means of electrochemical methods using  
118 carbon bare electrodes or carbon modified electrodes. It is noteworthy that some articles  
119 referred to the screen-printed electrode commercially available from Dropsens (inexpensive  
120 and reliable), but no one used the experimental conditions tested in this study (pH,  
121 connection with the mobile PalmSens device, useable for lab work – on turn connected either  
122 to a laptop or to a remote system in the field). As far as we know, the second experiment  
123 tested in this research is the first that uses a data reporting method analysed with this type of  
124 redox microelectrode for the analysis of GA antioxidant action.

125 In this study we attempt to fill in the gaps left by previously proposed methods found in  
126 the literature, recommending stable, fast, inexpensive and reproducible electrochemical  
127 detection methods to determine GA and its antioxidant power, in both standard and real  
128 samples. Our team, therefore, used two different electrochemical methods:

- 129 1) a new Lazar ORP-146C reduction-oxidation microsensor, coupled with a Jenco device to  
130 read potential GA applications, and for potential redox detection of GA, in order to  
131 estimate the antioxidant capacities of different electroactive media;
- 132 2) a commercially available screen-printed sensor linked to a PalmSens device, that uses  
133 carbon as a working electrode.

134 These two proposed methods were not tested before and are expected to have cost effective  
135 and excellent performances as to GA detection when compared with the previously reported  
136 chemically modified electrodes. The aim of this paper is, above all, to make use of the best  
137 conditions and to discuss those in which the pH of carrier solutions differed.

138

## 139 **2. Materials and Methods**

### 140 *2.1. Reagents*

141 A stock solution with a concentration of 0.1M was prepared using GA (Sigma Aldrich  
142 Corporation, Saint Louis, Missouri, USA) in distilled water. Buffer solutions with pH 5.8,  
143 7.0, and 8.0 were obtained by mixing, in different ratios, 0.1M solutions of sodium phosphate  
144 monobasic (Poch S.A, 44-101 Gilwice, Poland) and sodium phosphate dibasic (Poch S.A,  
145 44-101 Gilwice, Poland) (Ruffien-Ciszak et al., 2006).

### 146 *2.2. Equipment*

147 Differential pulse voltammetry experiments were carried out at room temperature, under  
148 dark conditions, using the electrochemical sensor interface PalmSens 3 (Palm Instruments  
149 BV, The Netherlands), controlled by a PC running PStTrace software version 4.7.  
150 Single-compartment three-electrode transducers DRP C110 (DropSens, Llanera, Spain) were  
151 used. These are screen-printed carbon electrodes with a ceramic substrate: L33 x W10 x H0.5  
152 mm with electric contacts made of silver, carbon (4 mm diameter) as the working electrode, a  
153 counter electrode also of carbon and a reference electrode made of silver (Gruene et al.,  
154 2018).

155 Redox measurements were taken with a Jenco device (Jenco Instruments, San Diego,  
156 California, USA), Model: 6230N coupled with a redox microsensor - ORP-146C (Shelf  
157 scientific, Lazar Research Laboratories, Inc., Los Angeles, CA, USA). An extremely small  
158 size sensor, with an electrode tip diameter of only 1 mm, it is used for large or small volumes  
159 (5  $\mu$ L) (<http://www.shelfscientific.com/cgi-bin/tame/newlaz/redoxn.tam>).

160 The Lazar Model ORP-146C micro oxidation-reduction electrode utilizes a specially  
161 formulated platinum redox sensing element, in conjunction with a silver/silver chloride  
162 reference electrode, to measure the oxidation-reduction potential in solution volumes down  
163 to 10 microliters. The microelectrode has both the redox sensor and the reference electrode  
164 built into a single electrode body. The reference junction is a fluoropolymer film, and the  
165 electrode flexible capillary stem is also composed of a fluoropolymer formulation. The  
166 reference solution storage compartment uses an epoxy body. The micro redox electrode has a

167 range of measurement of oxidation-reduction potential from -1500 mV to +1500 mV.  
168 Accuracy of the micro redox electrode is +/- 0.5 mV.

### 169 *2.3. Methods*

170 The GA stock solution in a 0.1M concentration was obtained fresh before each  
171 experiment. Presence of GA was tested in 10 mL buffers with different pH values (pH 5.8; 7;  
172 8), raising the concentration of the active compound to 2 mM. Each solution was tested,  
173 using the previously described method (Miccoli et al., 2018) in duplicate and the data were  
174 analysed (in order to work with average values and their standard deviations). Differential  
175 pulse voltammetry (DPV) was used and all parameters were established using PStTrace  
176 software: potential range (-1.0 V to 1.0 V), step potential 0.005 V, pulse potential 0.049 V,  
177 pulse time 0.05 s and scan rate 0.01 V/s. A diagram presenting the steps of the procedure is  
178 presented in **Figure 1**.

179 All redox data, collected by the portable microsensor, were obtained simultaneously  
180 with the electrochemical measurements (DPV), and under the same experimental conditions  
181 (using the same Berzelius glass), for better data correlation. The solution was stirred for 10s  
182 before the beginning of each survey, using a magnetic stirrer. Standard GA solutions were  
183 analyzed first, in order to obtain the calibration curves. The possible interferences in the  
184 presence of ascorbic and/or caffeic acid were analysed under the same conditions. Detection  
185 in real samples (homemade white wine, commercial green tea and apple juice) was  
186 undertaken using DPV method while homemade white wine and serum were detected using  
187 redox microsensor system

### 188 *2.4. Data registration*

189 Experimental DPV data were plotted as specific voltammograms. Data was obtained  
190 using PStTrace v4.7 software concerning the potential of area, specific peaks and peak height.  
191 These parameters were considered for data interpretation and qualitative-quantitative  
192 analysis. The portable microsensor directly indicated the potential equivalent to the redox  
193 reaction from that system.

194 All experimental data were stored, and all graphics were created with Microsoft Office  
195 Excel, using specific experimental values.



196

197 **3. Results**198 *3.1. Quality assurance for testing different solutions using the differential pulse voltammetry*  
199 *method*

200 The DPV parameters were previously optimized in the lab (data not shown). As  
201 mentioned in the description of working procedures, the potential range went from -1.0 V to  
202 1.0 V. However, based on the experimental results the method was optimized to include  
203 peaks of interest and to minimize total time of analysis. Data representation reflected a  
204 potential range from -0.5 V to 0.6 V.

205 The GA solutions, in concentrations of 0.1 to 2 mM in the buffer system, and with a pH  
206 5.8, were analysed and specific voltammograms were recorded. Though the total recording  
207 was for a potential range of -1.0 V to 1.0 V, the voltammograms were represented within the  
208 range of -0.1 V to 0.5 V (**Figure 2**), the range in which characteristic GA peaks were  
209 obtained. No peaks were recorded for a potential higher than 0.5V. A single peak  
210 corresponding to GA was observed. The average potential for peaks corresponding to GA at  
211 pH 5.8 was  $0.180 \pm 0.021$  V. Peak height and area were plotted against GA concentration to  
212 obtain calibration lines (**Figure 3**). Good calibrations were obtained with a linearity range of  
213 0.1 to 2.0) mM. The coefficients of determination were calculated with good results. Similar  
214 experiments were conducted for pH 7. The corresponding voltammograms and calibration  
215 curves are indicated in **Figure 4**.

216 Two peaks were observed corresponding to the GA in phosphate buffer pH 7 at  $0.175 \pm$   
217  $0.024$  V (main peak) and at  $0.465 \pm 0.056$  V (smaller), respectively. The characteristic values  
218 of the peaks (height and area) were plotted against the GA concentration in **Figure 5**.

219 Presence of GA at pH 8 and its potential quantification were also tested. The differential  
220 pulse voltammograms and calibrations are indicated in **Figure 6** and **Figure 7**. In **Figure 8**  
221 two peaks are observed. The average peak potentials corresponding to the GA in phosphate  
222 buffer pH 8 are  $-0.037 \pm 0.003$  V and  $0.137 \pm 0.017$  V, respectively.

223 Specific linear relationships of steady-state currents (peak height and peak area) against  
224 GA concentrations (0.1 to 0.8 mM) in buffer at pH 8 were observed for both potentials in

225 which peaks appeared. Above this concentration no linearity was observed. We proposed two  
226 ways to quantify the GA concentration, using peak height and peak area for each pH. Based  
227 on the standard deviation (SD) of response and the slope of the dependencies, the limit of  
228 detection (LOD) and limit of quantification (LOQ) were calculated, using a previously  
229 described method (Shrivastava and Gupta, 2011). Calibration lines and correlation  
230 coefficients ( $R^2$ ) are indicated in Figures 3, 5 and 7; LOD, LOQ and sensitivity (slope of  
231 calibration line) for each experimental situation are systematized in **Table 1**.

232 The measurement chain has a specific impact on data reports. The optimization steps  
233 that take into consideration diffusion and chemical reaction, as well as the  
234 adsorption/desorption inherent in any sensor, all contribute to an applied potential which  
235 starts at -0.5 V. Response time ( $t_{90, \max}$ ) was calculated as the time necessary to obtain 90% of  
236 the maximum response value (peak), as similar studies have previously indicated (Ziaian et  
237 al., 2015).

238 GA, as well as caffeic and ascorbic acids, all at the same pH values, were tested to obtain  
239 data concerning selectivity of the methods developed for a similar active compound  
240 concentration (0.3 mM). The results concerning the potentials corresponding to the DPV  
241 peak of these compounds are indicated in **Table 2**.

### 242 3.2. *Quality assurance for detection using redox microsensors*

243 The linear correlation between concentration and redox potential in GA solutions  
244 detected by microsensor are presented in Figure 8 (a-c). The sensitivity values which depend  
245 on pH values are depicted in **Table 3**. All the results are in accordance with previous  
246 experiments, when the DPV method was used for GA detection (increasing sensitivity from  
247 pH 5.8 to 8).

248 This technique enabled rapid, accurate, and non-invasive determination of the total  
249 antioxidant capacity of GA solutions, with results obtained in under 45 seconds, similar to  
250 the results reported in other studies using cyclic voltammetry, where the responding time was  
251 1 min (Xiong et al., 2017).

### 252 3.3. *Analysis of real samples*

253 In order to evaluate the real application of the proposed electrochemical methods, GA

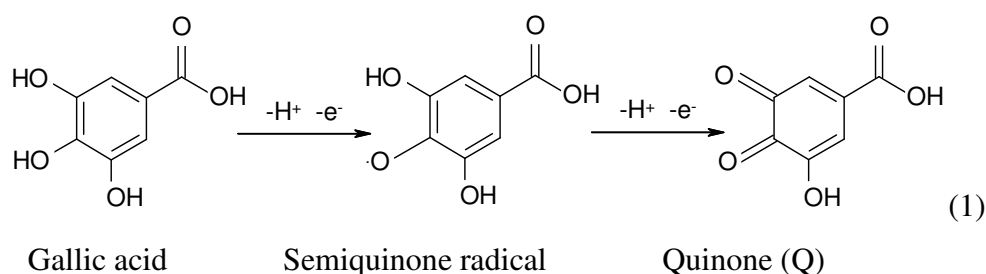
254 equivalents were assessed in white wine, green tea, apple juice (using DPV method) and in  
 255 red wine and human serum sample (using redox microsensor). The experiments were  
 256 performed in triplicate. The results were compared with DPPH  
 257 (1,1-diphenyl-2-picrylhydrazyl) method (Di Lorenzo et al, 2017; Liu et al., 2013). The  
 258 standard addition method was used, and the corresponding results are indicated in **Table 4**  
 259 and **Table 5**. Highly significant correlations were found between DPV and DPPH  
 260 ( $R^2=0.9977$ ) and between redox microsensor and DPPH ( $R^2=0.9998$ ) (**Figure 9** a, b).

261

#### 262 4. Discussion

263 GA is an electroactive compound, characterized by specific redox reactions due to  
 264 electroactivity resulting from the presence of three hydroxyl groups in the aromatic structure.  
 265 The two GA hydroxyl groups are deprotonated while two electrons and two protons are  
 266 generated; the GA is irreversibly oxidized first into a semiquinone radical and then into  
 267 quinone, according to the equation below (1). The electron exchanges are monitored in the  
 268 mentioned electrochemical detections because the current response is proportional to the GA  
 269 concentration.

270



271

272

273 Several studies have reported on the behaviour of different electrochemical compounds  
 274 (Bungau et al., 2017; Miccoli et al., 2018; Badea et al., 2017; Rauf et al., 2016) and on the  
 275 quantity of key phenolic compounds contributing to the total antioxidant capacity of wines  
 276 (Photinon et al. 2010; Makhotkina and Kilmartin, 2009; Sousa et al., 2004). The main  
 277 advantage in differential pulse techniques consists in the measurements of  $\Delta i/\Delta E$  value,  
 278 where  $\Delta i$  represents the difference between current intensity values, measured before and  
 279 after the pulse period (Wang et al., 2012). Another important feature of differential pulse  
 280 voltammetry is that the double intensity measurement offers peak-shaped results for intensity

281 dependence versus potential, with a maximum position correlated with the analyte type, and  
282 a height depending on the concentration of the active compound (Bungau et al., 2017;  
283 Miccoli et al., 2018; Badea et al., 2017; Sochor et al., 2013). An earlier study by Friedman  
284 and Jürgens (2000) which demonstrates that caffeic, chlorogenic, and gallic acids are not  
285 stable with respect to high pH and that the pH- and time-dependent spectral transformations  
286 are not reversible, led us to study, as well, the possible GA detection in different buffers (pH  
287 5.8; 7; 8). Our findings are similar to other previously reported data for GA detection using  
288 different methods and/or electrodes (**Table 6**).

289 The results obtained with screen-printed carbon electrodes and a portable PalmSens  
290 system) enabled us to detect GA in all three pH conditions, at room temperature in the dark.  
291 We also exploited the area under the anodic current wave as in other studies (Chevion et al.,  
292 2000), considering it a suitable parameter similar to peak current intensity, as the total  
293 antioxidant capacity of the sample. It appears that for GA, the phosphate buffer pH 7.0  
294 indicated the best analytical detection for the first specific signal,  $0.175 \pm 0.024$  V. Both the  
295 linearity established for a wide range of concentrations (0.1 - 2.0 mM) and the stability of the  
296 sample were good. Both calibration lines (using peak height and area) indicated low LOD  
297 and LOQ values. The GA tested in buffer pH 8.0 indicated two different peaks that can be  
298 used for future detection studies, but for a reduced range of linearity (0.1 - 1.0 mM and 0.1 -  
299 0.8 mM for peak height and area, respectively) it showed the same previously tested  
300 experimental conditions (pH 5.8; 7). The results obtained in pH 5.8 conditions are good and  
301 acceptable (low LOD and LOQ values); the sample is slightly more stable than in the other  
302 experiments (only one significant peak was found) due to the medium-acidity of the buffer.

303 It must be underlined that the appearance of peaks determines improvement in  
304 resolution and indicates greater sensitivity versus cyclic voltammetry. Also, to be stressed is  
305 that microsensors are important in real complex matrices such as those from fruits and their  
306 juices (Blasco et al., 2004), as well as in alcoholic beverages such as wines (Aguirre et al.,  
307 2010). The electron transfer from electroactive compounds in aqueous solutions to the  
308 electrode surface is important for a high-performance electrochemical sensor and must offer  
309 a proper affinity and good electronic conductivity (Kahl et al., 2014).

310 As most antioxidant molecules have functional groups with acid-based properties  
311 (hydroxyl, carboxyl), we also tested the pH influence on the GA analytical signal. Research  
312 in the field (Arteaga et al., 2012) has indicated that the peak potential values tended to  
313 become less positive as the pH values increased, and electro-oxidation took place more  
314 easily. Certain studies have reported GA as using electro-oxidation on a carbon nanotube-  
315 modified carbon paste electrode, in a buffer solution with pH 2.50, at 350 mV using Ag/AgCl  
316 as the reference electrode (Carneiro et al., 2018).

317 As in our study, Carneiro et al. (2018) obtained a voltammetric response in GA  
318 detection, using microfluidic electro-analytical devices made on a 3D printer (using ABS  
319 polymer-acrylonitrile butadiene styrene, combined with cotton yarns as microchannels).  
320 Used as an electrochemical detector, these devices demonstrated that the electrochemical  
321 oxidation of GA is characterized by two irreversible anode peaks, the first being attributed to  
322 the formation of the semiquinone radical, followed by oxidation in its quinone form (Yilmaz  
323 et al., 2013). Similarly to ours, these studies also showed that when the carrier buffer pH  
324 increased, the peaks (obtained using voltammetry) shifted to less positive potentials,  
325 indicating an easier electron donation.

326 Differential pulse polarography in 0.04 M Britton-Robinson buffer (pH 10.0) indicated  
327 high sensitivity for GA determination as a standard phenolic antioxidant. For analysis at -160  
328 mV potential, low interferences were observed with other compounds: ascorbic, oxalic,  
329 benzoic, tartaric and ethylenediamine tetra-acetic acids that made this technique useful for  
330 fruit juice analysis. The peak potential dependence on pH showed two linear portions broken  
331 at pH = 10.5, which corresponds to the GA pKa value that is related to its acid dissociation  
332 constant (Vilian et al., 2018). As Table 3 shows, ascorbic and caffeic acids did not interfere  
333 with DPV detection of GA in terms of selectivity, a conclusion similar to ones reached in  
334 other experiments using salt-templated 3D porous carbon electrode (Vilian et al., 2018).

335 For analysis of the second sets of experimental data (presented in Figure 8.a-c),  
336 detection of GA antioxidant status using the Lazar Model ORP-146C micro  
337 oxidation-reduction electrode, indicated good linearity ranges, depending on the pH value of  
338 the media (Table 3) due to its different redox reactivity. The fluoropolymer capillary tube of

339 the microsensor device makes it unbreakable; being more stable than the glass electrodes it  
340 thus contributes to a much more stable redox reading. The microsensor can also be connected  
341 to a computer, thus the redox potential can be continuously monitored on a PC and a real time  
342 curve registered if necessary  
343 (<http://www.shelfscientific.com/cgi-bin/tame/newlaz/redoxn.tam>).

344 Use of this type of microsensor is rapid for sample analysis and can be applied even to  
345 small sample volumes since the immersion depth for the micro-redox electrode is 0.5 mm. It  
346 can thus be used in 96 well plates, micro test tubes, serum cups and in capillary, NMR and  
347 microcentrifuge tubes. LOD and LOQ values calculated for GA detection were higher than  
348 with the previously tested method using DPV. This method made it possible to indicate only  
349 the potentials corresponding to electroactive solutions as their total antioxidant status. This  
350 will also be important in real samples (extracts, wines), when mixtures of electrochemical  
351 compounds are included.

352 The redox microsensor has also shown good results in estimating the antioxidant  
353 capacity index of real samples of white wine and serum. In this situation, similar to other  
354 methods used for detection of total antioxidant capacity/status (Di Lorenzo et al, 2017), the  
355 real sample data for quantitative estimation of antioxidants is reported as a GA equivalent  
356 (GAE) (using interpolation by means of a calibration line constructed on a GA concentration  
357 base) as recommended in the literature (Sen and Sarkar, 2013). Ideal for measuring the  
358 midpoint potential of cytochromes, this redox microsensor may be used successfully in  
359 different areas such as biotechnology, biomedical sciences and pharmaceutical or  
360 environmental studies.

361 The novelty of the results obtained in these studies consists in the possible use of the  
362 electroanalytic devices in point-of-care applications or in rapid food analysis control, without  
363 pre-treatment of surface electrodes (Randviir et al., 2013; Metters et al., 2012; Metters et al.  
364 2011). Since the components (carbon screen-printed sensors and Lazar microsensors) are  
365 commercially available, the devices and the proposed methods may be used by scientists in  
366 analytical laboratories. However, if the surface electrode undergoes modifications and  
367 microsensor characteristics thus improved, costs will naturally rise, and the sensors may

368 become too expensive for some laboratories. The significance of the electrochemical results  
369 was demonstrated in previous studies through correlation studies with the results obtained  
370 with conventional spectrophotometric assays for polyphenols using Folin-Ciocalteu  
371 procedure (absorbance at 280 nm) (Sanchez et al, 2013), classical spectrophotometric ABTS  
372 assay (Chaisuksant et al., 2012) or DPPH method (Di Lorenzo et al., 2017). For our studies, a  
373 spectrophotometric method with DPPH (as validation procedure) was used, as previously  
374 validated for wine samples (Di Lorenzo et al., 2017). Highly statistic correlations were  
375 obtained between DPV and DPPH ( $R^2=0.9977$ ) and between redox microsensor and DPPH  
376 ( $R^2=0.9998$ )

377 The proposed electrochemical protocols for both tested methods are facile, fast and offer  
378 the possibility of GA sensing with deviations (RSD%) less than 9% in repeatability between  
379 measurements. The reproducibility of GA detection by means of screen printed electrodes  
380 was studied using seven electrodes and the relative standard deviation (RSD) was 4.36%.  
381 The methods were validated by analysing real samples: wine, green tea, apple juice and  
382 serum fortified with GA. The results obtained are similar to other reports (Di Lorenzo et al.,  
383 2017; Fernandes and Salgado, 2016). Advantages and drawbacks of these two methods are  
384 presented in **Table 7**.

385

## 386 **5. Conclusions**

387 We have studied two types of devices that may be used for GA detection: Lazar  
388 ORP-146C reduction-oxidation microsensors coupled with a Jenco device to read potential  
389 applications for estimation of antioxidant capacities of different electroactive media, and  
390 screen-printed carbon sensors coupled with a mobile PalmSens device using differential  
391 pulse voltammetry for qualitative and quantitative GA detection. As it is well known, this  
392 electrode is cost effective and gives an excellent performance for GA detection when  
393 compared with other previously reported chemically modified electrodes.

394 To the best of our knowledge, it is the first time that the electrochemical methods proposed in  
395 this study, under experimental conditions mentioned above, are published in the scientific  
396 literature. Compared to optical, mass and thermal sensors, they seem more attractive due to

397 their remarkable detectability, experimental simplicity and low cost. The suggested methods  
398 show many advantages such as fast responses, low detection limits, wide dynamic ranges,  
399 and good selectivity in applications demonstrated with a white wine sample. Our results  
400 demonstrated a promising feature for diverse life science applications (environmental,  
401 clinical, cosmetic, agricultural), thanks to the very good calibration lines obtained for  
402 different pH values, with GA being used as the reference standard and results expressed as  
403 GA equivalents.

404

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410

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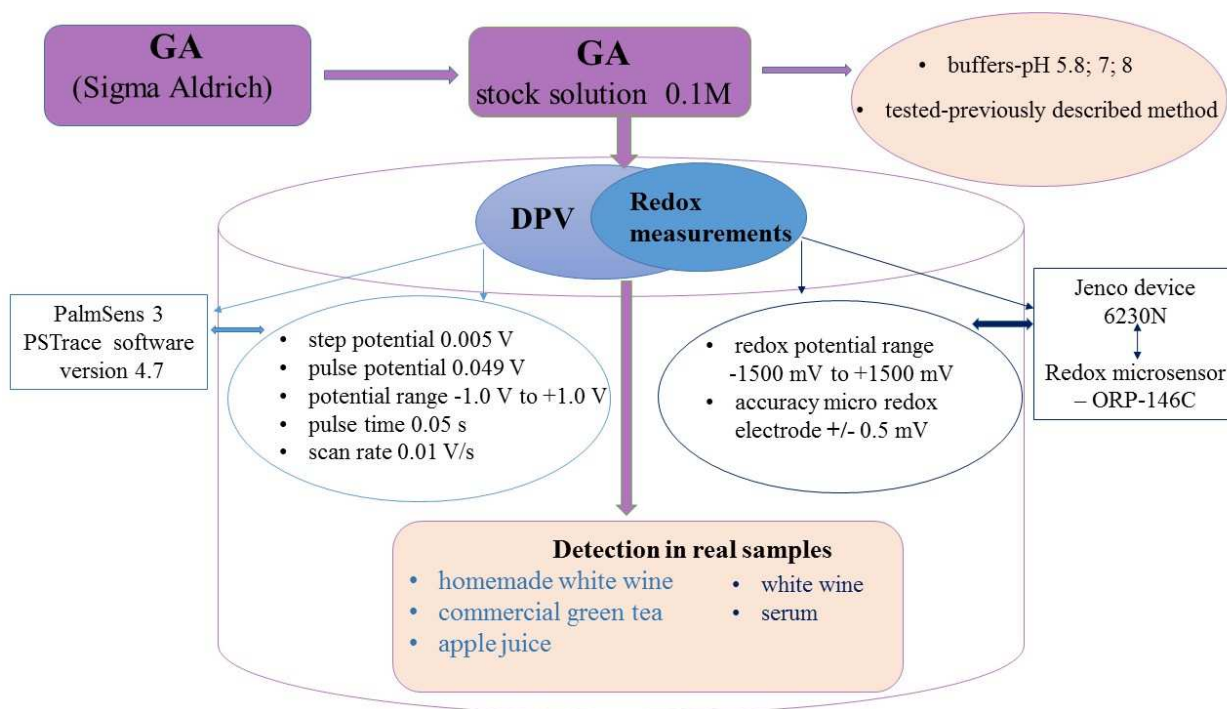
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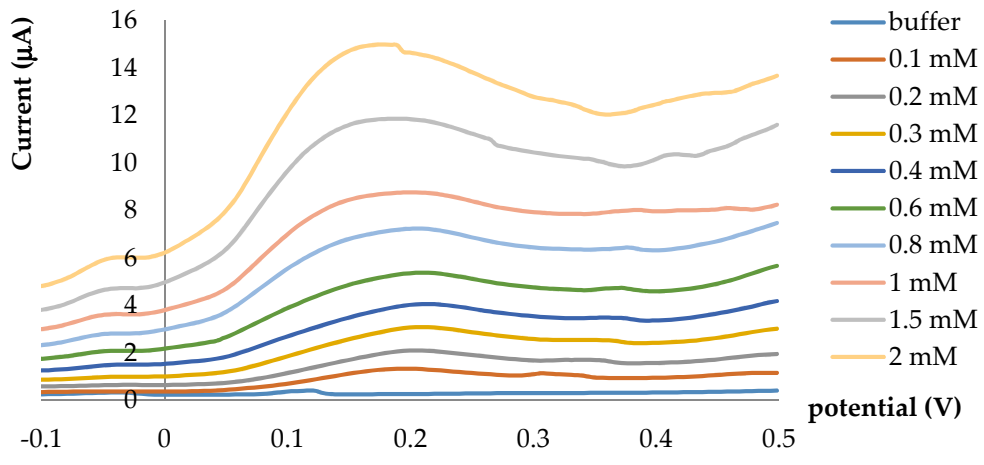
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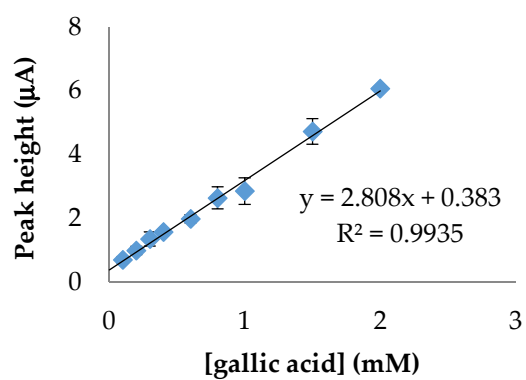
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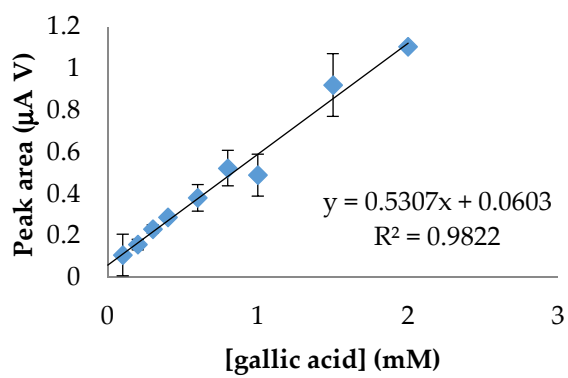
**Figure 1.**



**Figure 2.**

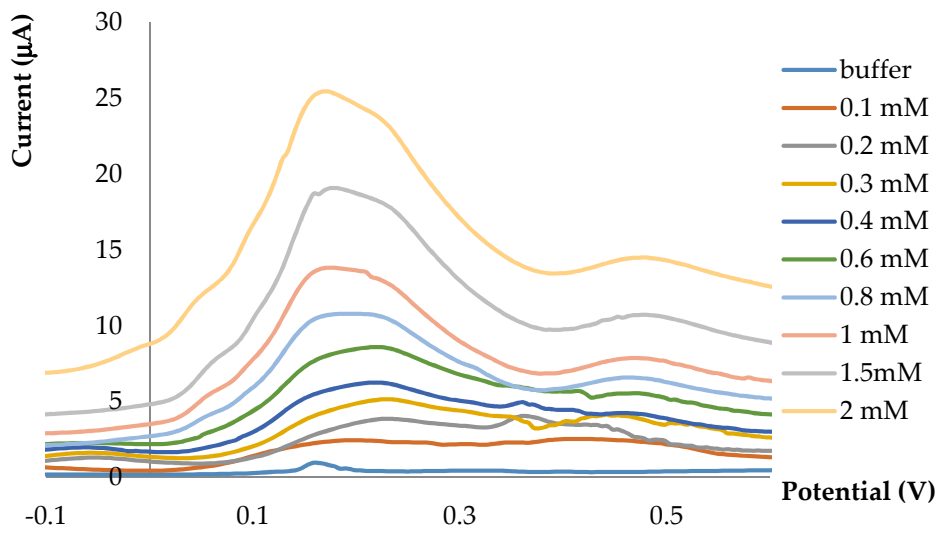


(a)



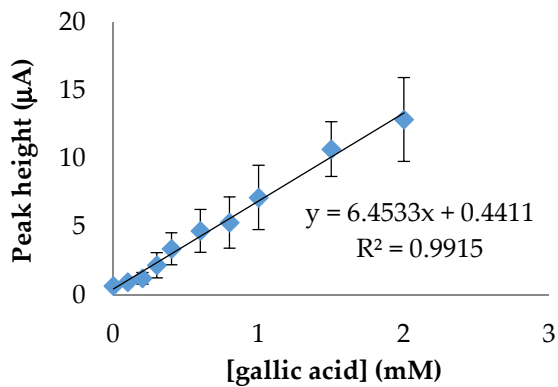
(b)

**Figure 3.**

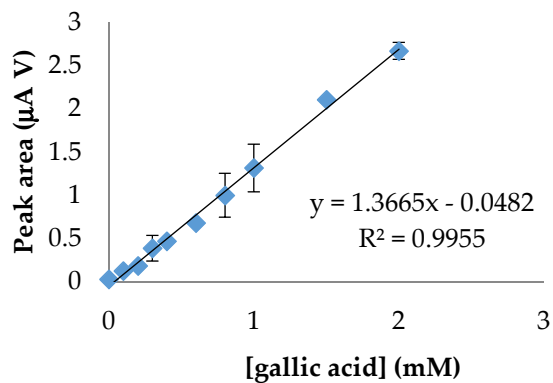


**Figure 4.**

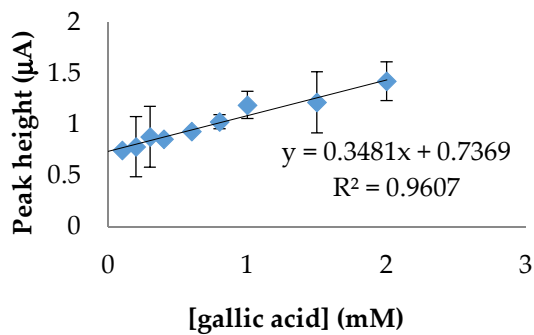




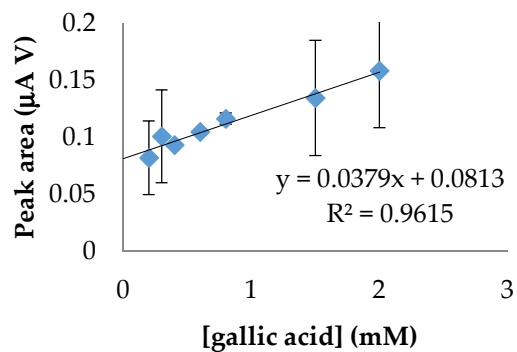
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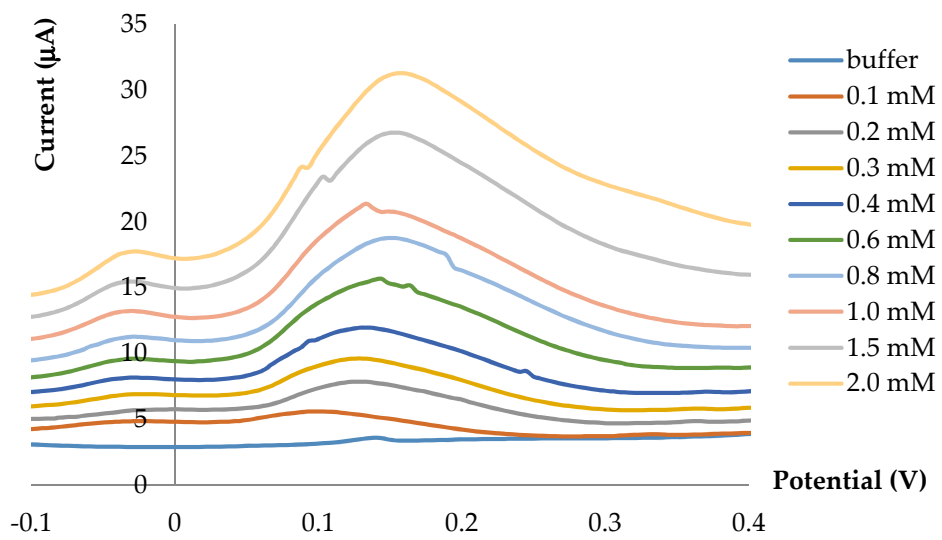


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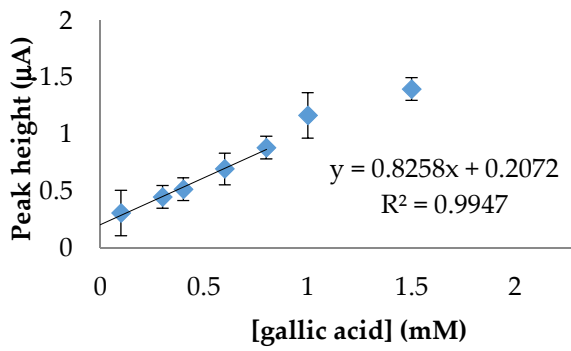


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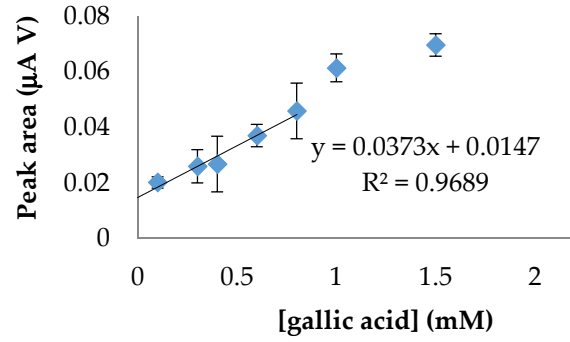
Figure 5.



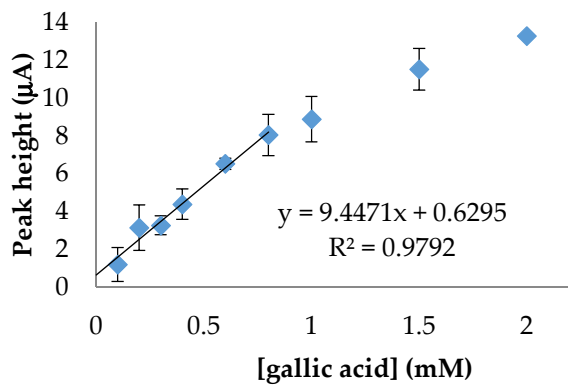
**Figure 6.**



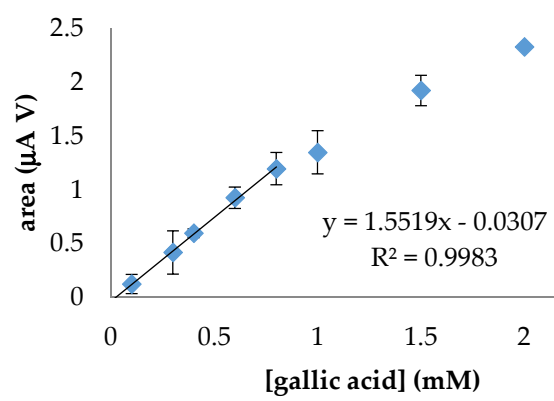
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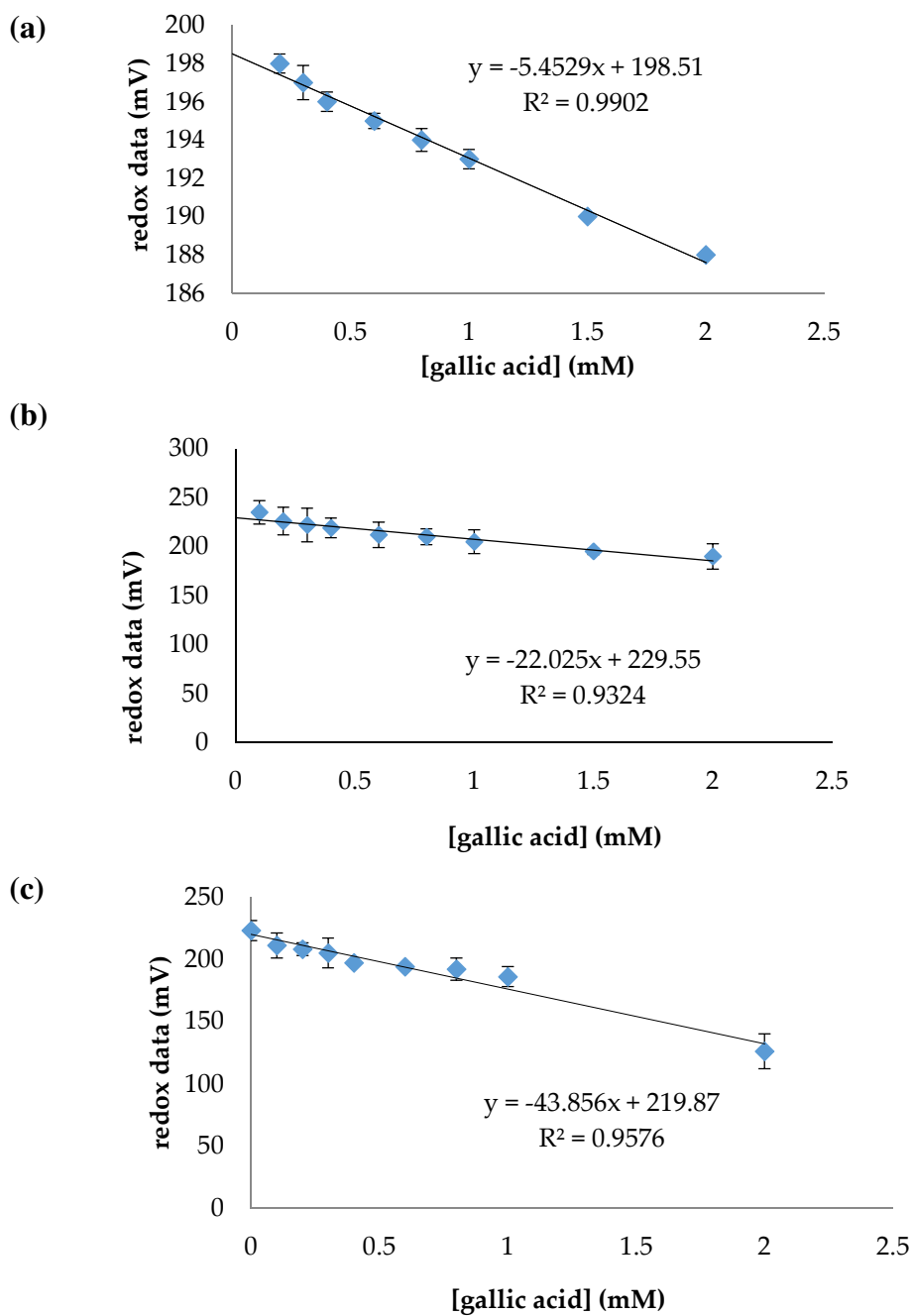


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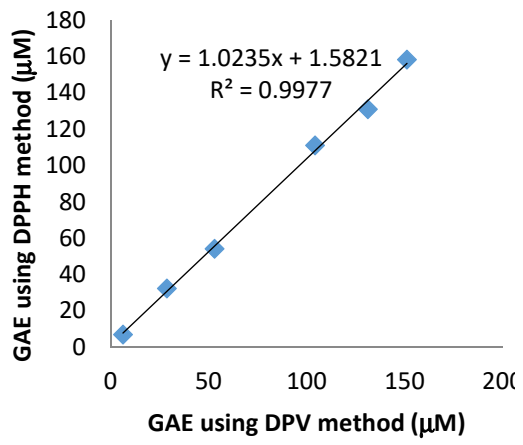


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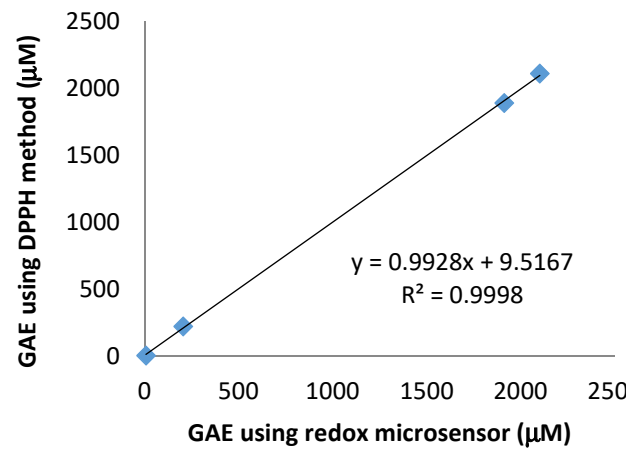
**Figure 7.**



**Figure 8.**



(a)



(b)

**Figure 9.**

**Table 1.** Characteristics of DPV experiments for detection of GA (peak heights and areas) measured with screen-printed carbon electrodes, at different pH values

pH	Principal Potential (V)	Linearity range (mM)	Calibration based on	R2	Sensitivity	LOD (mM)	LOQ (mM)	$t_{90, \max}$ (s)
5.8	0.180±0.021	0.1-2.0	Peak height	0.9935	2.808 $\mu\text{A}/\text{mM}$	0.033	0.099	66.2±1.89
			Peak area	0.9822	0.5307 $\mu\text{A}\cdot\text{V}/\text{mM}$	0.055	0.165	
7	0.175±0.024	0.1-2.0	Peak height	0.9915	6.4533 $\mu\text{A}/\text{mM}$	0.032	0.096	65.75±2.16
			Peak area	0.9955	1.3665 $\mu\text{A}\cdot\text{V}/\text{mM}$	0.023	0.070	
	0.465±0.056	0.1-2.0	Peak height	0.9607	0.348 $\mu\text{A}/\text{mM}$	0.082	0.248	91.85±5.04
			Peak area	0.9615	0.0379 $\mu\text{A}\cdot\text{V}/\text{mM}$	0.102	0.310	
8	-0.037±0.003	0.1-1.0	Peak height	0.9947	0.8258 $\mu\text{A}/\text{mM}$	0.066	0.201	46.67±0.27
			Peak area	0.9689	0.0373 $\mu\text{A}\cdot\text{V}/\text{mM}$	0.096	0.354	
	0.137±0.017	0.1-0.8	Peak height	0.9792	9.447 $\mu\text{A}/\text{mM}$	0.058	0.176	62.33±1.53
			Peak area	0.9983	1.5519 $\mu\text{A}\cdot\text{V}/\text{mM}$	0.046	0.138	

**Table 2.** Potentials for the peak of DP voltammogram (V) for gallic, caffeic, and ascorbic acids (0.3 mM) detection

<b>pH</b>	<b>Potentials for peak of DP voltammogram (V)</b>		
	<b>Gallic acid 0.3 mM</b>	<b>Caffeic acid 0.3 mM</b>	<b>Ascorbic acid 0.3 mM</b>
5.8	0.199±0.012	0.116±0.004	- 0.0136±0.001
7	0.189±0.014 0.453±0.014	0.057±0.001	0.0498±0.004
8	-0.034±0.002 0.133±0.012	0.121± 0.004	0.089±0.003

**Table 3.** Characteristics of GA detection using redox microsensors, at different pH values

<b>pH</b>	<b>Linearity range (mM)</b>	<b>R<sup>2</sup></b>	<b>Sensitivity (mV/mM)</b>	<b>LOD (mM)</b>	<b>LOQ (mM)</b>
5.8	0.2-2	0.9902	-5.4529	0.049	0.148
7	0.1-2	0.9324	-22.025	0.109	0.331
8	0.1-1.5	0.9576	-43.856	0.074	0.223



**Table 4.** Detection of gallic acid in real samples (N=3) using DPV method with carbon screen printed electrodes, pH 7

Sample	Spiked sample GA ( $\mu\text{M}$ )	Content determination					
		DPV method			DPPH method		
		Total found ( $\mu\text{M}$ ) mean( $\pm\text{SD}$ )	Recovery degree (%)	RSD (%)	Total found ( $\mu\text{M}$ ) mean( $\pm\text{SD}$ )	Recovery degree (%)	RSD (%)
White wine*	0	6.1( $\pm 0.5$ )	-	8.2	7.0( $\pm 0.3$ )	-	4.3
	100	104.2( $\pm 1.1$ )	98.2	1.1	111.2( $\pm 0.4$ )	103.9	0.4
Green tea juice**	0	28.5( $\pm 0.7$ )	-	2.5	32.4( $\pm 0.6$ )	-	1.9
	100	131.2( $\pm 0.8$ )	102.1	0.6	131.1( $\pm 0.5$ )	99.0	0.4
Apple tea juice**	0	52.8( $\pm 1.2$ )	-	2.2	54.3( $\pm 0.8$ )	-	1.5
	100	151.1( $\pm 0.7$ )	98.9	0.5	158.5( $\pm 0.8$ )	102.7	0.5

\* Homemade wine; \*\*sample from local supermarket

**Table 5.** Detection of gallic acid in real samples (N=3) using spiked procedure and corresponding recovery, with redox microelectrode, at pH 5.8

Sample	Spiked sample GA ( $\mu\text{M}$ )	Content determination					
		Redox microelectrode method			DPPH method		
		Total found ( $\mu\text{M}$ ) mean( $\pm\text{SD}$ )	Recovery degree (%)	RSD (%)	Total found ( $\mu\text{M}$ ) mean( $\pm\text{SD}$ )	Recovery degree (%)	RSD (%)
White wine	0	6.4( $\pm 0.5$ )	-	7.81	7.0( $\pm 0.3$ )	-	4.28
	200	204.2( $\pm 0.5$ )	98.9	0.24	223.8( $\pm 0.4$ )	108.1	0.18
Serum	0	1912.3( $\pm 0.7$ )	-	0.04	1890.5( $\pm 0.6$ )	-	0.04
	200	2100.8( $\pm 0.7$ )	109.9	0.04	2110.2( $\pm 1.2$ )	100.9	0.06

**Table 6.**

<b>Electrode</b>	<b>Method</b>	<b>Sample</b>	<b>Characteristics</b>	<b>Reference</b>
A functionalized graphene oxide/poly(p-amino-hippuric acid)-sodium dodecyl sulfate nanocomposite modified glassy carbon electrode (APTS@GO/PPAH-SDS/GCE)	CV (cyclic voltammetry), DPV (differential pulse voltammetry), amperometry	Black tea Tab water	Linear range of 0.006-2000 $\mu\text{M}$ ; LOD 1.7 nM for GA (S/N=3) using amperometric method; Determination in the as real samples	(Baghayeri et al., 2018)
Carbon paste electrode (CPE) modified by nanocomposite containing zirconia nanoparticles (ZrO <sub>2</sub> NPs), choline chloride (ChCl) and gold nanoparticles (AuNPs) to construct ZrO <sub>2</sub> -ChCl-AuNPs/CPE	DPV	Green tea Fruit juice Human urine samples	Linear response 0.22- 55 $\mu\text{M}$ ; LOD 25 nM; Applied for the independent simultaneous determination of GA and UA (uric acid)	(Shahamirifard et al., 2018)
Modified GC electrodes (titanium nitride) or wolfram carbide-doped reduced graphene oxide, labeled as TNrGO and WCrGO, respectively	CV	Sweet wines	LOD 1.1 $\mu\text{M}$ and 3.1 $\mu\text{M}$ for TNrGO and WCrGO, respectively; Linear ranges: for TNrGO 4.5-76 $\mu\text{M}$ and for WCrGO 10-100 $\mu\text{M}$	(Stanković et al., 2017)
Glassy carbon electrode modified with multi-walled carbon nanotubes and poly-quercetin (polyquercetin/MWNT/GCE)	DPV	Tea	The linear dynamic range 10-750 $\mu\text{M}$ ; LOD 0.10 $\mu\text{M}$ ; The tea antioxidant capacity evaluation (AOC).	(Ziyatdinova et al., 2017)
Organic electrochemical transistors (OECTs) based on poly(3,4-ethylenedioxythiophene): poly (styrene sulfonic acid) (PEDOT: PSS) Functionalizing the gate electrodes of the OECTs with nanocomposites of poly (diallyl	Doping/de-doping of the channel upon gate polarization	Tea	LOD 10 nM of GA; Rapid and accurate assessment of total phenol content of practical tea samples	(Xiong et al., 2017)

dimethylammonium chloride) (PDDA) and multiple carbon nanomaterials				
Activated screen printed carbon electrode (ASPCE)	Amperometry	Green tea Apple juice	Linear range 0.01-1799.6 $\mu\text{M}$ LOD 0.031 $\mu\text{M}$	(Raja et al., 2017)
Multiwalled carbon nanotube-modified carbon paste electrode (MWCNT-CPE), and MIP and MWCNT-modified CPE (MIP-MWCNT-CPE)	Electrochemical detection	Apple, pineapple, orange juices A commercial green tea drink	Nano-sensors (MIP-MWCNT-CPE) have higher sensitivity compared with bare CPE, MWCNT-CPE, and MIP-CPE; Linear range 0.12-380.0 $\mu\text{M}$ LOD 47.0 nM	(Shojaei et al., 2016)
Glassy carbon electrode modified with cerium dioxide nanoparticles in a 0.02 M BrijA(R)35	DPV	Spices	pH 7.4; Analytical range 50-2490 $\mu\text{M}$ ; LOD 11.9 $\mu\text{M}$	(Ziyatdinova et al., 2016)
A modified electrode prepared by modification of the CPE with graphene nano-sheets	DPV	plant samples	Analytical range 0.3-150 $\mu\text{M}$ ; LOD 0.11 $\mu\text{M}$	(Sheikh-Mohseni, 2016)
Gold micro-clusters (AuMCs) electrodeposited on sulfonate functionalized graphene (SF-GR) electrode	DPV	Black tea Cortex mouton Urine samples	pH 4; Linear range 0.05-8.0 $\mu\text{M}$ ; LOD 10.7 nM	(Liang et al., 2016)
Single-walled carbon nanotubes (SWCNT) covalently functionalized with polytyrosine (Polytyr)	Amperometry	Tea extracts	Linear range 0.5- 170 $\mu\text{M}$ ; LOD 8.8 nM Determination of total polyphenolic	(Eguílaz et al., 2016)
Thin electroactive poly(melamine) film immobilized on a pre-anodized screen-printed carbon electrode (SPCE*/PME)	FIA (flow-injection amperometry)	Green tea	Linear response to GA in pH 3 and pH 7.0; LOD 0.076 $\mu\text{M}$ ; RSD 3.9% is obtained for 57 successive measurements of 50 mM GA in pH 7	(Su and Cheng, 2015)
Gel-RGONS modified glassy carbon electrode (Gel-RGONS/GCE)	LSV (linear sweep voltammetry)	Black tea	Linear response 1.0 – 100 $\mu\text{M}$ ; LOD 0.47 $\mu\text{M}$	(Chekin et al., 2015)

The hybrid material of chitosan (CS), fishbone-shaped Fe <sub>2</sub> O <sub>3</sub> (fFe(2)O(3)), and electrochemically reduced graphene oxide (ERGO) modified glassy carbon electrode	DPV	Red / white wines	Linear relationship with the logarithmic values of GA concentration over the range from 1-100 $\mu$ M; LOD 0.15 $\mu$ M; Antioxidant capacity index of real samples	(Gao et al, 2015)
SiO <sub>2</sub> nanoparticle modified carbon paste electrode using multiwalled carbon nanotubes (MWCNTs) and graphite	Electrochemical	Tea Orange juice samples	Concentration range 0.8 – 100 $\mu$ M; LOD 0.25 $\mu$ M; Sensitivity 1790.7 $\mu$ A/mM	(Tashkhourian and Nami-Ana, 2015)
Electrochemical sensor based on [Cu(2)tpmc](ClO <sub>4</sub> )(4) immobilized in PVC matrix and coated on graphite (CGE) or glassy carbon rod (CGCE)	DPV	White, rose and red wine samples	Voltammograms for both sensors, recorded in HNO <sub>3</sub> (supporting electrolyte), at pH 2 and analytical range 0.25-100 $\mu$ M; 2 linear calibration curves (for higher and lower GA concentration range); LOD for CGE 0.148 $\mu$ M; LOD for CGCE 4.6 $\mu$ M; Determination of the antioxidant capacity based on GA equivalents for	(Petković et al., 2015)
Electro-generated o-dianisidine derivative (o-DD)-stabilized multi-walled carbon nanotube (MWCNT)-modified glassy carbon electrode (GCE/o-DD@MWCNT)	Chronoamperometry	Real grape juice Water samples	Detection at 0.16 V vs. Ag/AgCl in pH 7 PBS; Sensitivity 0.4580 $\mu$ A / $\mu$ M; Detection range of 100-1300 $\mu$ M; LOD 144 nM	(Sundaram et al., 2015)
Electrochemical sensor based on poly-epinephrine /glassy carbon electrode, PEP/GCE	AdSV (adsorptive stripping voltammetry)	Black tea sample	Linear range 1.0 - 20.0 $\mu$ M LOD 0.663 $\mu$ M	(Abdel-Hamid et al., 2013)
Glassy carbon (GC) or platinum (Pt) working electrode	CV amperometry	Tea	Optimum response at pH 5.8; Linear range 1-250 $\mu$ g/mL; LOD 2.34 $\mu$ g /mL	(Sen and Sarkar, 2013)

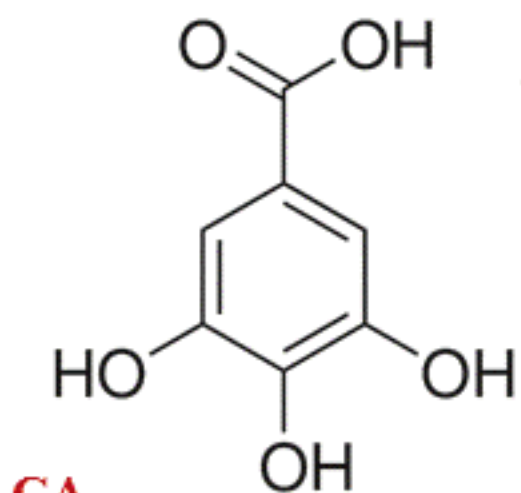
			Quantitative estimation of antioxidants in samples were expressed as gallic acid equivalent (GAE)	
Modified carbon paste electrode was prepared by incorporating the TiO <sub>2</sub> nanoparticles in the carbon paste matrix	CV DPV EIS	Black/green teas	Buffered solutions with pH 1.7 Linear dynamic range 2.5 -150 μM; LOD 0.94 μM	(Tashkhourian et al., 2013)
Glassy carbon working electrode	CV and flow injection with amperometric detection (FI-AD)	Ginger infusion	pH 7.0; Antioxidant capacity of real sample was expressed as gallic acid equivalent (GAE) unit	(Chaisuksant et al., 2012)
Glassy carbon electrode	Flow-based coupled electrochemical technique - sequential injection (SI) with AD	Commercial instant ginger infusion beverages	pH 7.0; GA used as standard antioxidant and the capacity reported as gallic acid equivalent (GAE) unit	(Chan-Eam et al., 2010)
Sensor based on a modified carbon paste electrode with multi-walled carbon nanotubes	CV chronocoulometry, LSV, DPV disk electrode voltammetry	<i>Punica granatum</i> , <i>Myrtus communis</i> , <i>Itriphal extracts</i>	LOD 0.2 μM	(Ghoreishi et al., 2011)
Working electrodes - carbon paste electrodes (CPEs) prepared from 3 types of carbonaceous materials: graphite (G-CPE), carbon microspheres (μS-CPE) and carbon nanotubes (CNT-CPE); the reference electrode - Ag AgCl/KCl sat. and the counter	CV	No real samples tested	An array of electrodes has been constructed using the three types of electrodes. LOD: 11.32 μM - G-CPE; LOD: 13.24 μM – μS-CPE; LOD: 13.26 μM - CNT-CPE.	(Apetrei et al., 2011)

electrode - platinum plate				
Screen printed carbon electrode DRP C110	DPV	White wine Green tea Apple juice	LOD: 23-103 $\mu\text{M}$ (depending on pH – Table 1)	Our work
Redox microsensor - ORP-146C	Redox measurements	White wine Serum	LOD: 49-109 $\mu\text{M}$ (depending on pH –Table 3)	Our work

**Table 7.** Advantages/drawbacks of the methods

	<b>DPV method</b>	<b>Redox microsensor</b>
Advantages	Working at different pH values: 5.8; 7; 8 Low LOD and LOQ Commercially available electrode Possibility to be used in telemonitoring (remote system) – PalmSens device with Bluetooth Fast Inexpensive Reproducible Applicable: case of biological samples Selective versus caffeic and ascorbic acid	Working at different pH values: 5.8; 7; 8 Low LOD and LOQ Commercially available electrode Portability – redox potential can be continuously monitored on a PC and a real time curve can be obtained Unbreakable because of fluoropolymer capillary tube of the microsensor device Fast Inexpensive Reproducible Applicable: case of biological samples Reusable electrode
Drawbacks	Single use electrode	Not selective – it could indicate the total antioxidant power/capacity, in GAE





Stock solution 0.1M

Jenco device + new  
microsensor device

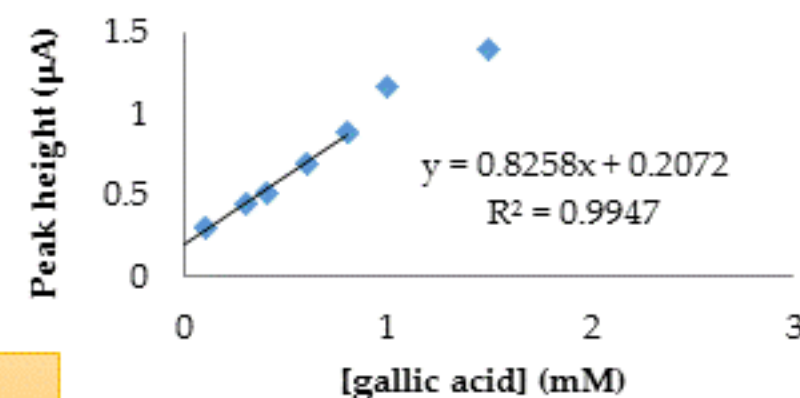
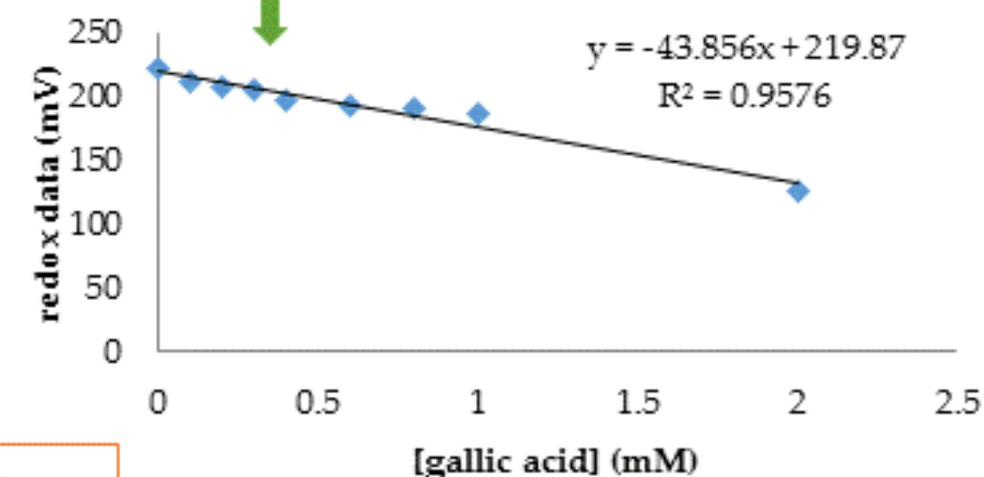
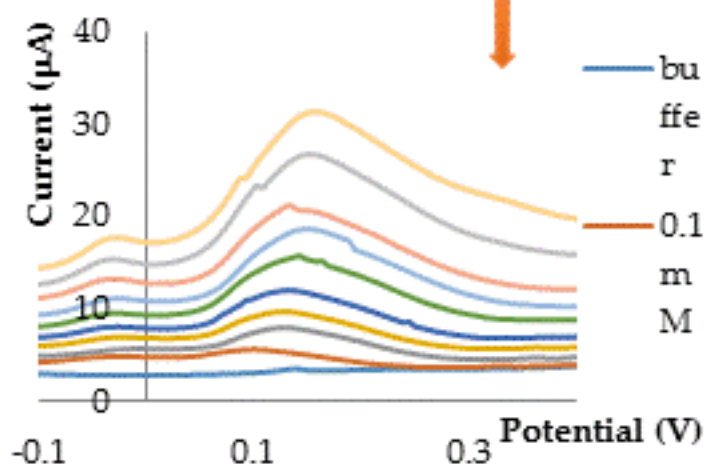
Estimate antioxidant capacities  
of different electroactive media

pH	Linearity range (mM)	R <sup>2</sup>	Sensitivity (mV/mM)	LOD (mM)	LOQ (mM)
5.8	0.2-2	0.9902	-5.4529	0.049	0.148
7	0.1-2	0.9324	-22.025	0.109	0.331
8	0.1-1.5	0.9576	-43.856	0.074	0.223

pH values of 5.8, 7, and 8  
Two different electrochemical methods

Carbon screen-printed sensors  
mobile PalmSens

Qualitative and quantitative  
detection of GA



The procedures could be further applied in other clinical, food or environmental analyses.