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# Electrochemical Determination and Antioxidant Capacity Modulation of Polyphenols in Deep Eutectic Solvents.

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KEYWORDS. Deep eutectics, polyphenols, electrochemistry, antioxidant capacity, long-term stability.

**ABSTRACT.** Deep eutectic solvents (DES) are currently developed as ecofriendly and efficient solvents for polyphenols extraction. However, a challenge remains in these processes concerning the polyphenols determination that is routinely performed through colorimetric Folin-Ciocalteu assays. Besides these assays use toxic reagents, they may have serious limitations in some DES media due to possible side reaction or interferences with the DES components as found herein with ethaline (choline chloride / ethylene glycol (1:2)) or betaine/citric acid (2:3). An alternative method based on simple electrochemical analyses directly performed in DES-based media is proposed. Since the direct electrochemistry of polyphenols in DES has been hardly explored, 9 polyphenolic

standards including 7 flavonoids are examined and their electrochemical behaviour are found closely-related to those classically obtained in traditional solvents, notably in aqueous solutions. A linear relationship is obtained between concentration and peak current intensity for quercetin in the range  $10^{-5}$  -  $10^{-4}$  mol.L<sup>-1</sup>, demonstrating the potential of the method for polyphenols contents quantitation. More importantly, their antioxidant capacity is evaluated by differential pulse voltammetry (DPV) through the measurements of the redox potentials. An interesting variation is observed according to the nature of the DES components, suggesting that antioxidant activity of polyphenols can be modulated through the choice of the DES. Moreover, a good stability of the polyphenols samples in the DES-water mixture under study is obtained after storage for 10 months at 30 ° C. These results open appealing perspectives in polyphenols extraction processes using eutectic solvents as extracting media that can be part of formulation for cosmetic or pharmaceutical applications, resulting in high-added values extracts.

## **INTRODUCTION**

There is currently much interest in the development of green and efficient processes for the extraction of natural products from biomass. In this context, the solvents used in the processes either as extracting medium or for the recovery of target compounds are of paramount importance since they represent the largest part of the waste mass and contribute to environmental pollution while potentially hazardous to human health. To overcome these issues, deep eutectic solvents (DES) have been gaining increasing attention as sustainable and safe solvents.<sup>1-3</sup> DES are generally viewed as mixture of two or three components whose melting temperature is lower than that of each individual component because the components are strongly interacting with each other, often through hydrogen bonding.<sup>1,4</sup> A stricter definition of DES has been recently proposed as a mixture of two (or more) compounds for which the melting temperature corresponding to an eutectic point

temperature is below that of an ideal liquid mixture with a significant negative deviation from ideality.<sup>5</sup> DES are generally considered as greener and cheaper alternative to ionic liquids and share many physico-chemical properties with them, notably a great solubilizing power.<sup>1</sup> However, they are much easier to synthesize, involving cheap biosourced and/or biocompatible components. They are then regarded as biocompatible, biodegradable and non-toxic materials, even if this last point probably requires further dedicated investigations.<sup>6-7</sup> Thus DES have been successfully employed to substitute conventional volatile organic solvents in the extraction of various bioactive natural compounds including polyphenols.<sup>4</sup> Polyphenols are an important class of phytochemicals which are widely distributed as secondary metabolites in edible and non-edible plants.<sup>8</sup> They have a wide range of biochemical activities, especially their antioxidant activity.<sup>8</sup> The beneficial effects of the antioxidant properties for human health are nowadays known to a large public,<sup>9</sup> and attract growing interest in the fields of cosmetics, pharmaceuticals and nutraceuticals whose industries are in demand of natural, greener and safer ingredients. This has led to the development of sustainable extraction methods where DES may improve the greenness and cost-effectiveness of the process. Even more important than increasing extraction yields, the preservation of the bioactivity of the generated extracts and their non-toxicity are highly desirable, along with the option of keeping the DES itself as an active ingredient. This would result not only in an environmental friendly and safe approach but also in high added-value extracts. In this context, some works has reported improvement of stability or bioactivity thanks to DES.<sup>10-14</sup> In addition, DES are nowadays considered in pharmaceutical science as part of the therapeutic formulation not only because they could advantageously increase the solubility of molecules and even macromolecules (proteins, nucleic acids, polysaccharides) of pharmaceutical interest compared to the aqueous media but also

bring interesting properties such as antimicrobial activity, enhancement of drug bioavailability.<sup>7,</sup>

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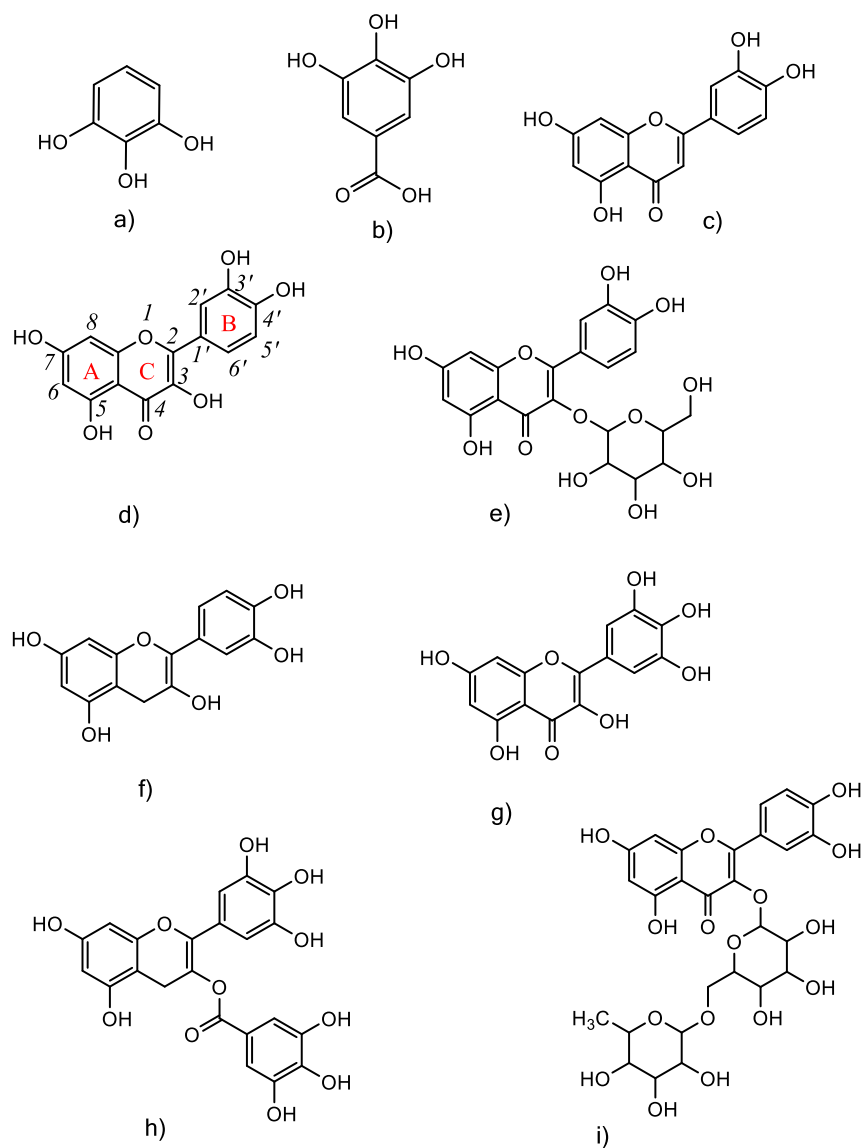
However, a challenge concerns the quantification and identification of polyphenols in DES extracts which could still be regarded as the weak link in the whole extracting process. Usually, the quantification and/or identification are carried out with analytical chromatography techniques (HPLC, gas chromatography, with different detection systems),<sup>16</sup> or with colorimetric assays as classically employed in conventional media (Folin-Ciocalteu, FRAP, etc).<sup>17</sup> Chromatography analyses are the most reliable tool to both identify and quantify the phenolics present in the extracts by establishing the phenolic profile with a great precision. But they require heavy equipment and trained operators. Consequently, for a quick determination of the total amount of phenolics contained in the extracts, colorimetric assays especially Folin-Ciocalteu assay are preferred as a routine method because they are quick and easy to handle.<sup>17-18</sup> A huge volume of data is based on this assay including those concerning DES extracts. Although that Folin-Ciocalteu assay is widely accepted as a method to determine the total phenolic content, it overestimates the phenolic content because of the low selectivity of Folin-Ciocalteu reagents and possible interference of any reducing substrates.<sup>17-18</sup> Especially, many components of DES could potentially interfere with reagents and make the colorimetric assay inaccurate.

Electrochemical techniques represent an alternative and powerful strategy for determining the polyphenols contents because they allow a quick, simple, inexpensive and sensitive detection.<sup>19-20</sup> They do not require toxic reagents or complex sample preparation, even turbid solutions can be easily analysed. Moreover, another benefit of electrochemical approaches is the possibility to probe the overall reducing power of the polyphenols through the measurements of their redox potentials.<sup>21</sup> Low redox potential, i.e. a facile electron transfer, indicates a high

antioxidant activity. Worth is to mention that electron transfer is the conceptual base of several antioxidant capacity assays like FRAP but also Folin-Ciocalteu which could be formally seen as a measurement of the antioxidant capacity.<sup>18</sup> Compared to colorimetric assays involving various reagents, voltammetric analyses can be considered as a direct evaluation of the antioxidant activity that depends on the physico-chemical properties of the active compounds. In addition, if the analyses are performed in the extracting media itself, possible interactions with the media could be probed since the electrochemical signal may be sensitive to specific solvation effects.<sup>22-23</sup>

Thus, electrochemical determination of polyphenols contents or antioxidant capacity have proved to be efficient, even in complex matrices, including honey,<sup>24</sup> human urine,<sup>25</sup> blood plasma,<sup>26</sup> or wine.<sup>27</sup> Surprisingly, there is no reported example of electrochemical analyses of polyphenols directly performed in DES. Only works based on the dilution in conventional aqueous electrolyte or the electrode drop-casting of DES containing polyphenols have been described to date.<sup>28-29</sup>

Herein, we examine the electrochemistry of phenolics in 3 DES media based on betaine and choline chloride. The phenolic compounds were chosen as standard and include 2 monophenols and 7 representative flavonoids, both aglycone or glycoside (Figure 1). The voltammetric signals are directly recorded in the DES-based media in order to show that electrochemical analyses could be a valuable alternative to Folin-Ciocalteu assay while the relevance of this colorimetric assay is carefully evaluated in the DES used in this work. In addition, the antioxidant capacity of the phenolics in the DES-based media is also discussed as a function of the DES nature, showing a potential synergy between DES and polyphenols. Finally, long-term storage of some flavonoids is also considered.



**Figure 1.** Chemical structure of monophenolics and polyphenols : a) pyrogallol, b) gallic acid, c) luteolin, d) quercetin, e) isoquercetin, f) catechin, g) myricetin, h) epigallocatechin gallate, i) rutin. Usual rings denomination, i.e. A, B, C is exemplified on the quercetin structure.

## EXPERIMENTAL SECTION

**Chemicals.** Pyrogallol, quercetin, (+)-catechin were purchased from Sigma-Aldrich. Gallic acid (98 %), myricetin, citric acid (99.6 %), choline chloride (99 %) and ethylene glycol (99.5 %) were from Acros. Betaine anhydre was supplied by TCI. Luteolin, isoquercetin and rutin were from

Merck, and epigallocatechin gallate from Alfa Aesar. All chemicals were used without further purification. DES with 30 % of water (w/w) were mixed with ultrapure water (18.2 MΩ).

**Synthesis of DES.** The choline chloride/ethylene glycol DES mixture was prepared with a molar ratio 1:2. The constituents were mixed under stirring at 80°C for 2 h until a stable clear homogeneous liquid was obtained. The betaine/citric acid DES mixture was prepared with a molar ratio 2:3, the constituents and water were mixed under stirring at 60°C for 4 h until a stable clear homogeneous liquid was formed. The DES were allowed to cool. The water content was determined by Karl Fischer titration (831 KF Coulometer with generator electrode with diaphragm) through an average of three measurements. Finally, the water content was adjusted to 30% of water (w/w).

**Folin-Ciocalteu assay.** Folin-Ciocalteu assay for total phenolic content was prepared and calibrated with phloroglucinol as a standard. 80 μL of sample, 520 μL of water and 40 μL of Folin-Ciocalteu's reagent were mixed with a vortex. After 1 min, 160 μL of 20% sodium bicarbonate solution was added to the mixture, then vortexed. The mixture is left at room temperature in darkness for 1h30. The absorbance was monitored at 760 nm with a spectrophotometer Fluostar Omega (BMG labtech).

**Preparation of the phenolics sample for electrochemistry measurements.** Except for myricetin for which 70 μmol.L<sup>-1</sup> solutions were prepared, the different phenol compounds were added in the 3 DES-based media for preparing aliquot solutions of concentration equal to 10<sup>-2</sup> mol.L<sup>-1</sup>. After vortexing, a ten-fold dilution of the aliquot is performed by adding DES media. A variation of the solubility of the compounds as a function of DES is observed (Table S1). Turbid but homogeneous solutions are generally obtained with BCA- water 30 % and ethaline-water 30



% except for pyrogallol and gallic acid. Clear solutions are obtained with “pure” ethaline. The  $10^{-2}$  mol.L<sup>-1</sup> aliquot solutions correspond to saturated conditions except for “pure” ethaline.

**Table 1.** Solubility appearance of the polyphenols solution in the 3 DES media.

Solubility appearance	QCT	LUT	ISOQCT	RUT	CAT	EGCG	AG	Pyrogallol
<b>BCA</b>								
10 <sup>-2</sup> M	turbid	turbid	turbid	turbid	soluble	turbid	soluble	soluble
« 10 <sup>-3</sup> M »	partially soluble	partially soluble	turbid	turbid	soluble	Partially soluble	soluble	soluble
<b>Ethaline-water 30 %</b>								
10 <sup>-2</sup> M	partially soluble	partially soluble	nd	turbid	partially soluble	nd	nd	soluble
« 10 <sup>-3</sup> M »	soluble	soluble	nd	partially soluble	soluble	nd	nd	soluble
<b>Ethaline</b>								
10 <sup>-2</sup> M	soluble	soluble	nd	soluble	soluble	nd	soluble	soluble
« 10 <sup>-3</sup> M »	soluble	soluble	nd	soluble	soluble	nd	soluble	soluble

QCT : quercetin ; LUT : luteolin ; ISOQCT : isoquercetin ; RUT :rutin ; CAT :catechin ; EGCG :epigallocatechin gallate ; AG :gallic acid.

**Electrochemical measurements.** The measurements were performed either with carbon screen printed electrodes (carbon SPE, DRP 110 - Dropsens) purchased from Metrohm or with an home-made three-electrode cell,<sup>30</sup> using a glassy carbon working electrode (disk of 1 mm of diameter), a platinum wire as a counter-electrode and a silver wire as a quasi-reference. A drop of 50  $\mu$ L of solution of phenolics in DES-based media was used with SPE allowing to cover the three

electrodes system while 200  $\mu\text{L}$  of solution was employed with the home-made cell. In this latter case, the glassy carbon electrode was carefully polished with a SiC paper and diamond paste (Struers), then extensively rinsed with ultrapure water and finally dried with an Argon flow prior to experiments. Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) were carried out with an Autolab PGSTAT 30 potentiostat/galvanostat (Metrohm Autolab B.V.). For CV, the potential was scanned between -0.5 to 0.8 V at  $0.1 \text{ V}\cdot\text{s}^{-1}$ . DPV measurements were performed with a step potential of 2.55 mV, a pulse amplitude of 50 mV, a pulse width of 30 ms and scan rate of  $4 \text{ mV s}^{-1}$ . Voltammetric scans were recorded between -0.5 to 1.2 V.

## RESULTS AND DISCUSSION

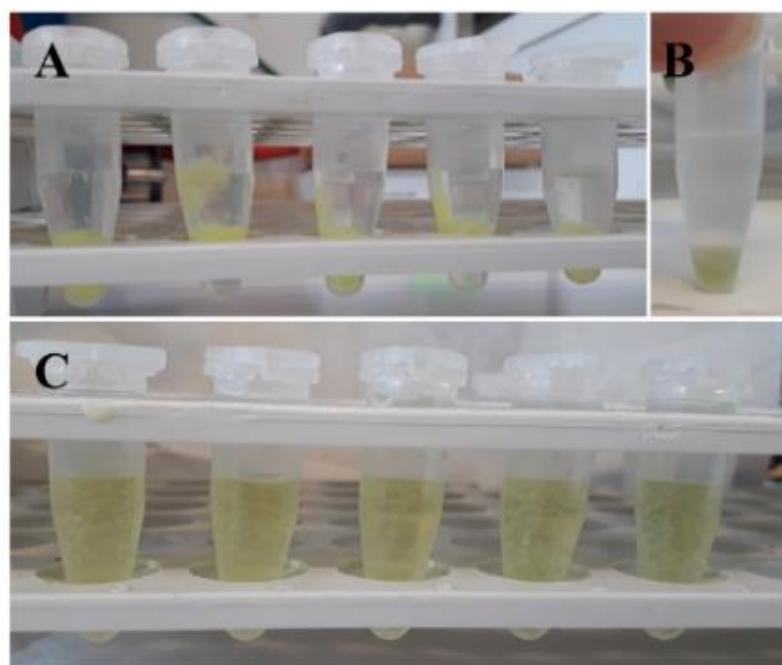
In this work, we consider 3 DES media based on 2 different DES: betaine/citric acid 2:3 (BCA) and ethaline (choline chloride/ ethylene glycol 1:2). While ethaline represents an archetypal DES, based on the classical choline chloride salt and used in a wide range of applications including extraction, BCA is more rarely employed despite its great potential. Interestingly, these DES, both biosourced, were chosen because of distinct structures, and different pH. BCA and ethaline are diluted with water and ethaline is also employed as “pure” material as explained in the following. BCA and ethaline are used as they contain a considerable amount of water i.e. 30 % (w/w). This amount is specifically chosen for lowering the viscosity of the solvents in the event of applications in extractions processes for which this parameter affecting transport phenomenon is of primary importance.<sup>4-5</sup> In a recent work, the effect of different concentration of water (10%, 30%, 75% w/w) in natural DES was evaluated in the extraction of flavonoids.<sup>31</sup> The best extraction yield is found for a water concentration of 30 % while extraction efficiency markedly decreases for further dilution. Similarly, 20 % of water (w/w) was found optimal for the extraction of rutin in choline

chloride-based DES.<sup>32</sup> The presence of such amount of water may drastically change the structure of DES, notably through hydrogen bonds disruption, leading to a loss of the supramolecular structure.<sup>33-34</sup> Interestingly, an NMR study of reline demonstrates that the hydrogen bonding structure subsists with addition of 14 % water (w/w) , with a full loss for concentration above 67 % (w/w).<sup>35</sup> The molar ratio of water which is compatible with the stability of DES actually depends on the nature of the DES composition.<sup>36</sup> However, many works have pointed out that dilution of water using a moderate concentration of water does improve the extraction efficacy,<sup>4</sup> and 30 % w/w of water is generally viewed as a maximum limit able to preserve the specific properties of DES towards extraction.<sup>2, 31-33, 37</sup> Ethaline with 0.86 % water, being an archetypal DES, is also used for comparison purposes. BCA-water 30 % exhibits a pH equal to 2.5 while ethaline and ethaline- water 30 % has pH equal to 7 and 7.3, respectively. Obviously, considering their structure, polyphenols properties are expected to be sensitive to pH. It is noteworthy, for instance, that their electrochemical behaviour are pH-dependent.<sup>20, 38-42</sup>

**Folin-Ciocalteu assay.** As explained in the introduction, Folin-Ciocalteu assay is routinely employed for determining the total phenolics content in extracts. As in conventional media, the method is equally widely used in DES extracts but there is a lack of critical assessment of the relevance of the method in DES. The Folin-Ciocalteu reagent (FCR) is prepared from a mixture of phosphomolybdic and phototungstic acids, with lithium sulfate that gives a yellow color to the solution. The exact chemical nature of the reagent is not known but probably based on heteropolyanions of phosphotungstates-molybdates.<sup>17-18</sup> Phenolic compounds can react with FCR under strong basic conditions, and pH is usually fixed at pH~10 using sodium carbonate. The reaction between phenols and FCR leads to an intense blue coloration which is

spectrophotometrically detected and, the corresponding absorbance is supposed to be proportional to the phenolics concentration. The blue color is believed to originate from species like  $(\text{PMoW}_{11}\text{O}_{40})^{4-}$  obtained from the reduction of FCR by phenolate compounds possibly through electron-transfer mechanisms.<sup>18</sup>

The two kind of DES used in this work are incompatible with FCR, precluding any reliable determination of phenolics content with Folin-Ciocalteu assay. Figure 2 clearly shows a precipitation of the FCR in the presence of ethaline. On the other hand, a side reaction occurs between FCR and BCA-water 30 %, notably due to the acidic character of the DES (Figure 2). These observations fully support the need for alternative methods dedicated to polyphenols quantitation or antioxidant activity evaluation because Folin-Ciocalteu assay may be particularly difficult if impossible to achieve with some DES.



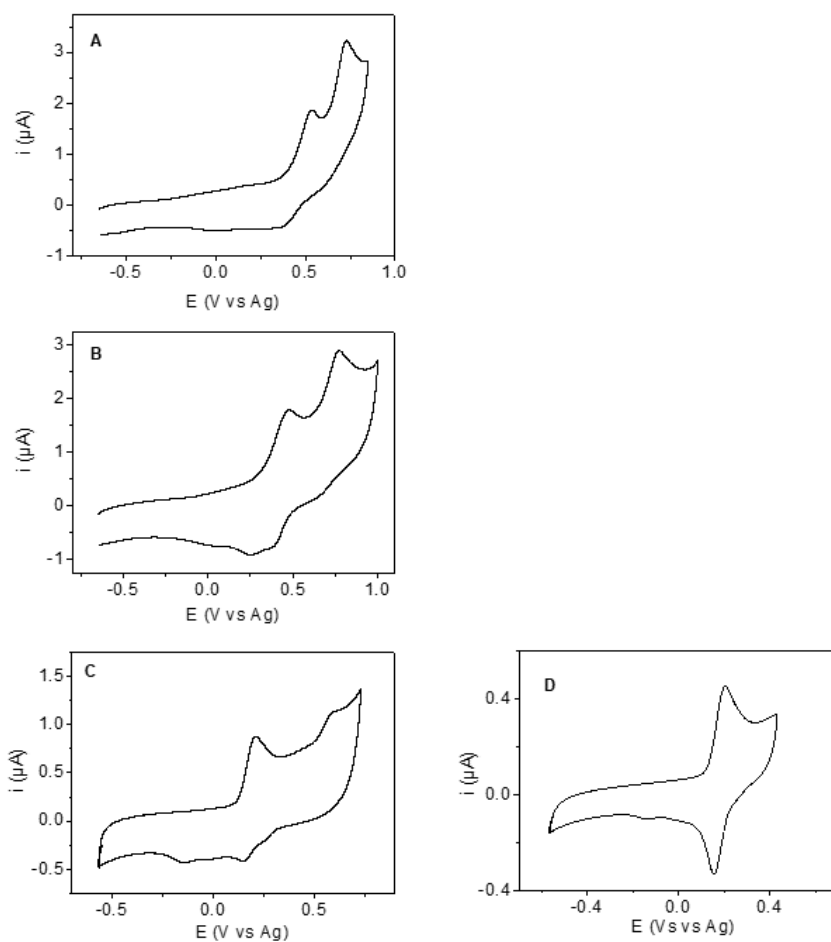
**Figure 2.** Folin-Ciocalteu assay with DES-based media containing 0, 25, 50, 75 and 100  $\mu\text{g/mL}$  of phloroglucinol standard, from left to right. (A) ethaline, (B) ethaline – water 30 %; (C) BCA-water 30 %

**Electrochemistry of phenolic compounds in the DES-based media.** First, cyclic voltammetry of various standard flavonoids is evaluated in the 3 eutectic mixtures. Figure 3 displays some typical voltammograms recorded with quercetin. The electrochemical signals are well-defined in all the media, indicating that the redox activity of flavonoids is efficiently detected in such DES-based media composed of an organic salt as hydrogen bond acceptor associated to an organic hydrogen bond donor (so-called Type III DES, <sup>4,43</sup>).

Actually, the electrochemistry of the different phenolics under study, especially the flavonoids has been widely studied in conventional media, <sup>38,44-45</sup> mainly in aqueous buffered solutions.<sup>40-42,46-53</sup> The electrochemical behaviour of flavonoids is related to the electroactivity of the A and B phenol units while ring C generally has much less influence (see Figure 1). In aqueous media, the redox behaviour of these units is characterized by proton-electron transfer mechanisms which depend on the pH. The first oxidation peak is generally due to B ring and corresponds to the oxidation of catechol or pyrogallol moiety. Due to electron delocalisation, the phenoxy radicals in B ring are relatively stabilized, therefore the oxidation process is quasi-reversible (Figure S1). An oxidation peak at more positive potentials is related to the oxidation of 5,7 substituent on the A ring (Figure 1). An additional peak due to the hydroxyl group at C3 position in the C ring may occur and is generally located at potentials between the two former. Typically, this peak is not observed for luteolin, rutin or isoquercetin.

In contrast to conventional media, less is known about the flavonoid electrochemistry in DES because they have been not yet explored in these media. We can only mention the electrochemical analysis of vanillic and caffeic acids dissolved in a DES (lactic acid: glucose: water) and drop-casted onto an electrode, immersed in a conventional electrolyte,<sup>29</sup> or quercetin studied in phosphate buffer containing 10 % of DES.<sup>28</sup> Although that some DES, notably type III DES, are

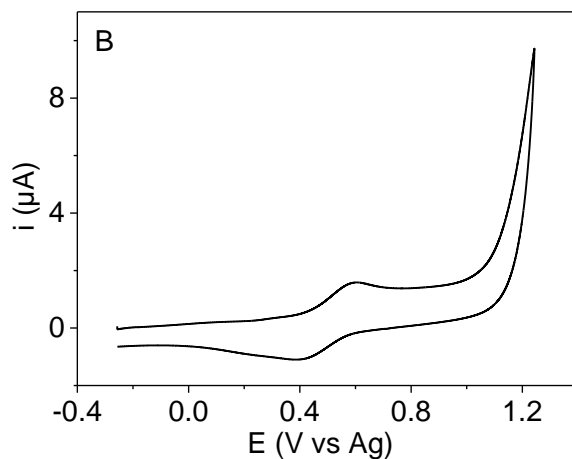
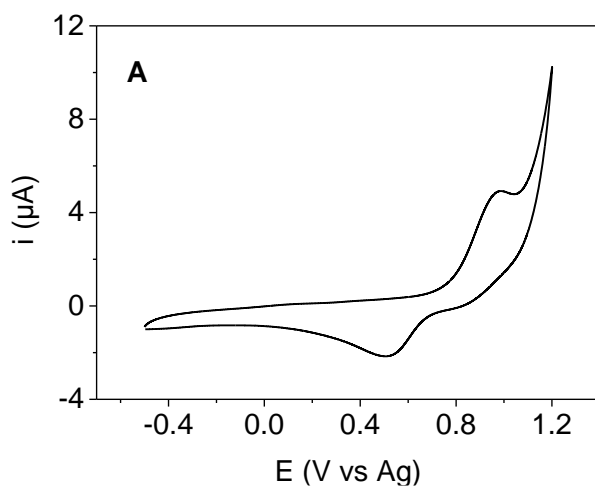
suitable media for performing electrochemical measurements,<sup>54-55</sup>, no study of flavonoids or related compounds has been carried out directly using DES as electrolyte.

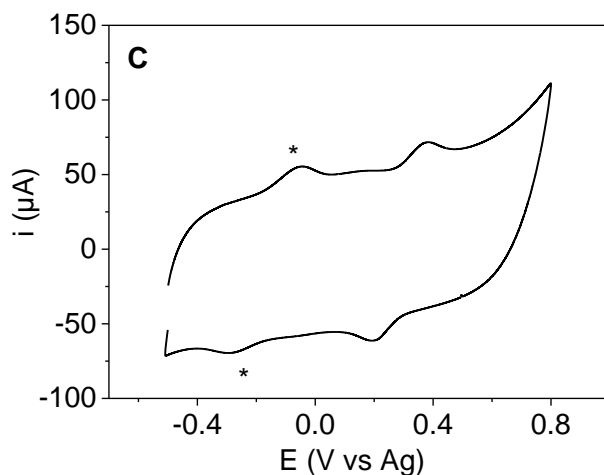


**Figure 3.** Cyclic voltammetry of quercetin at 0.2 V/s on a glassy carbon electrode ( $\varnothing$  1mm) in different eutectic mixtures (A) “pure“ ethaline (B) ethaline- water 30 % (C) and (D) BCA-water 30 %. (D) corresponds to a limited potential range, showing the reversibility of the first oxidation system.

The electrochemical behaviour of quercetin in the 3 DES-based media is comparable to those reported in aqueous media (Figure 3).<sup>40, 46, 53, 56</sup>. Two oxidation peaks are observed and could be attributed to the oxidation of 3',4'-dihydroxy substituent in B ring (first peak) and hydroxyl group

at C3 position in C ring (second peak). This assignment is further supported by the electrochemical behaviour of luteolin which displays only one peak (Figure 4). The oxidation associated to the A ring at higher potential is probably hidden by the oxidation of the DES. The oxidation potentials in ethaline or ethaline water 30 %, on the one hand and in BCA- water 30% on the other hand, are different, indicating that the redox behaviour of the flavonoid is probably sensitive to the DES composition and properties such as pH. This point will be further analysed below.





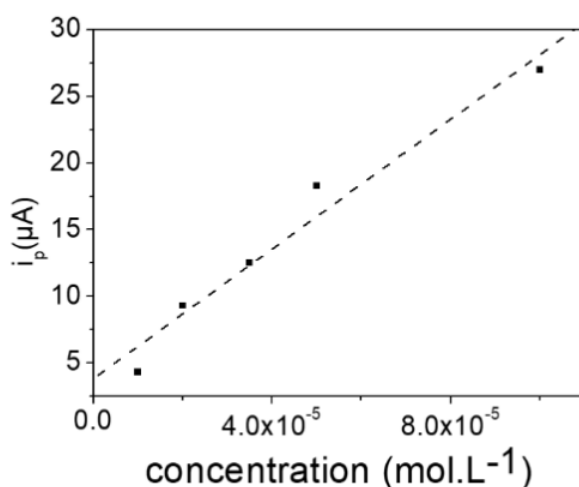
**Figure 4.** Cyclic voltammeteries of luteolin in A) ethaline, B) ethaline-water 30 % and C) BCA-water 30 %. A and B are recorded using home-made three-electrode cell while C is obtained at SPE electrode. \* are impurities present in the DES batch.

However, it is interesting to compare the values of oxidation potentials of quercetin obtained in ethaline and ethaline – water 30 % with those reported in aqueous solutions of same pH, i.e. pH=7. Peak potentials values of 0.15 V and 0.5 V vs Ag/AgCl were found in phosphate buffer solution,<sup>46</sup> while values equal to 0.53 and 0.48 V for the first peak and to 0.73 and 0.76 V for the second peak were obtained in “pure ethaline” and ethaline-water 30 %, respectively. These results show that oxidation of quercetin is more difficult to achieve in ethaline than in aqueous conventional medium, suggesting strong interaction between the DES components and the polyphenol.

Differential pulse voltammetry (DPV) is an electrochemical technique able to minimize the capacitive contribution in the current measurement. Thus DPV has a good sensitivity even at low concentration of analytes (typically  $10^{-7} - 10^{-8}$  mol.L<sup>-1</sup>). The technique has been largely employed in conventional media for polyphenols quantitation in extracts.<sup>19</sup> The characteristic response signal of DPV is a voltammogram with a peak whose intensity is directly proportional to the concentration of the analyte. As observed in Figure 5 with quercetin in BCA – water 30 %, a



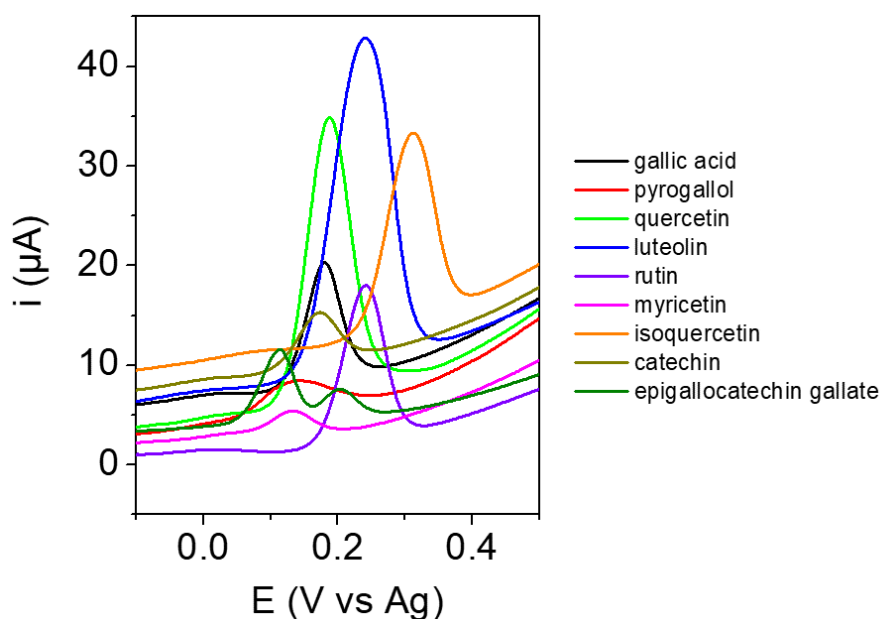
good linear correlation ( $r^2 = 0.98$ ) is obtained between the peak current intensity and the concentration of quercetin in the 10-100  $\mu\text{mol.L}^{-1}$  range. In this concentration range, quercetin is well soluble in the DES-based media (no apparent turbidity). Although that the concentration range might be overestimated compared to the expected amount of polyphenols in extracts, this result is very promising and validates the use of DPV as practical alternative to Folin-Ciocalteu assay for the quantitation of polyphenols in DES-based media. As an illustration, we have performed extraction of thyme and green tea in BCA-Water 30 % and the extracts were analyzed using DPV (Fig. S1). Oxidation peaks with intensity in the range 15-10  $\mu\text{A}$  are typically observed, suggesting that the amount of phenolics contained in the extracts could be evaluated by electrochemistry and expressed for instance as quercetin equivalents from calibration exemplified in Figure 5. Further work combining electrochemistry and chromatography of real extracts is currently in progress to fully evaluate the potential of the technique and will be published elsewhere.



**Figure 5.** Linear variation of oxidation peak current intensity (first peak) as a function of concentration of quercetin in BCA – water 30 % water. Concentration range [10-100  $\mu\text{mol. L}^{-1}$ ]

**Antioxidant capacity in DES-based media.** Importantly, electrochemical techniques have been also proved to be very efficient for evaluating and classifying the antioxidant capacity (antioxidant power) of phenolics compounds on the basis of the measurement of their redox potentials.<sup>19, 57</sup> It has been demonstrated that the lowest oxidation potential rules the antioxidant power.<sup>58-59 47, 60</sup> In other words, the ring leading to the radical with the lower redox potential corresponds to the active antioxidant moiety in any flavonoid. Indeed, the conjugation between the rings, especially B and A, in the flavonoid radicals is very inefficient. When B ring is a catechol or pyrogallol unit as for the flavonoids under study, it is responsible of the antioxidant action.<sup>60</sup> The lower the redox potential, the higher is the antioxidant capacity.

Therefore, we especially focus on the first oxidation peak in the following. DPV measurements in the 3 DES-based media were recorded for all the 9 standard flavonoids used in the work (Figure 6).



**Figure 6.** DPV signals at the first oxidation peak for 9 phenolics in BCA – 30 % water recorded with carbon SPE electrodes.

Table 2 gathers the values of the redox peak potentials obtained from DPV analyses. For each of the DES-based media, the redox potentials of the different flavonoids remain in the same range, in good agreement with their close chemical structure. Pyrogallol unit is known to oxidize at slightly lower potentials than catechol moiety, probably because of a better stabilization of the formed radicals thanks to additional hydroxyl group in B ring.<sup>47</sup>. Thus considering the series of flavonoids in BCA-water 30 %, it is not surprising that myricetin and epigallocatechin gallate exhibit slightly lower redox potentials than quercetin, rutin, isoquercetin or catechin. Note that the redox potentials of gallic acid and pyrogallol are in line with those of myricetin and epigallocatechin gallate.

**Table 2.** Peak potentials values obtained from DPV measurements corresponding to the first oxidation peak (V vs Ag)

Phenolics	Pure ethaline	Ethaline-water	BCA - water
GA	nd	nd	0.16
pyrogallol	nd	0.50	0.15
QCT	0.55	0.46	0.18
ISOQCT	0.66	0.59	0.31
LUT	0.71	0.48	0.25
RUT	0.68	0.44	0.24
myricetin	nd	nd	0.13
CAT	0.69	0.54	0.18
EGCG	nd	nd	0.11-0.20 <sup>a</sup>

GA, gallic acid; QCT, quercetin; ISOQCT, isoquercetin; LUT, luteolin; RUT, rutin; CAT, catechin, EGCG, epigallocatechin gallate. <sup>a</sup>the signal for EGCG is characterized by a “double” peak

The most interesting result is the variation of the redox potential according to the nature of the DES. There are striking differences when comparing values in ethaline or ethaline –water 30 % with those in BCA-water 30 %. The values in ethaline and ethaline – water 30 % are relatively close, with slightly lower values in ethaline-water 30 %, probably because of slightly higher pH in the water diluted DES.<sup>20</sup> In contrast, the redox potentials are negatively-shifted in BCA –water 30 %, indicating that the phenolics are much easier oxidized in BCA than in ethaline. This result is especially remarkable because the redox potentials of flavonoids are known to shift to more positive values as the pH is decreased. For instance, in aqueous electrolyte, the peak potentials of myricetin and rutin at pH = 7 were found at 0.05 and 0.25 V vs SCE, respectively while the values were 0.25 and 0.4, respectively at pH = 4.<sup>42</sup> A theoretical paper demonstrates that the antioxidant capacity of catechin increases as the pH increases.<sup>39</sup> In sharp contrast, the antioxidant activity of the 9 phenolics under study is clearly higher in the acidic BCA DES-based medium than in the two neutral ethaline media.

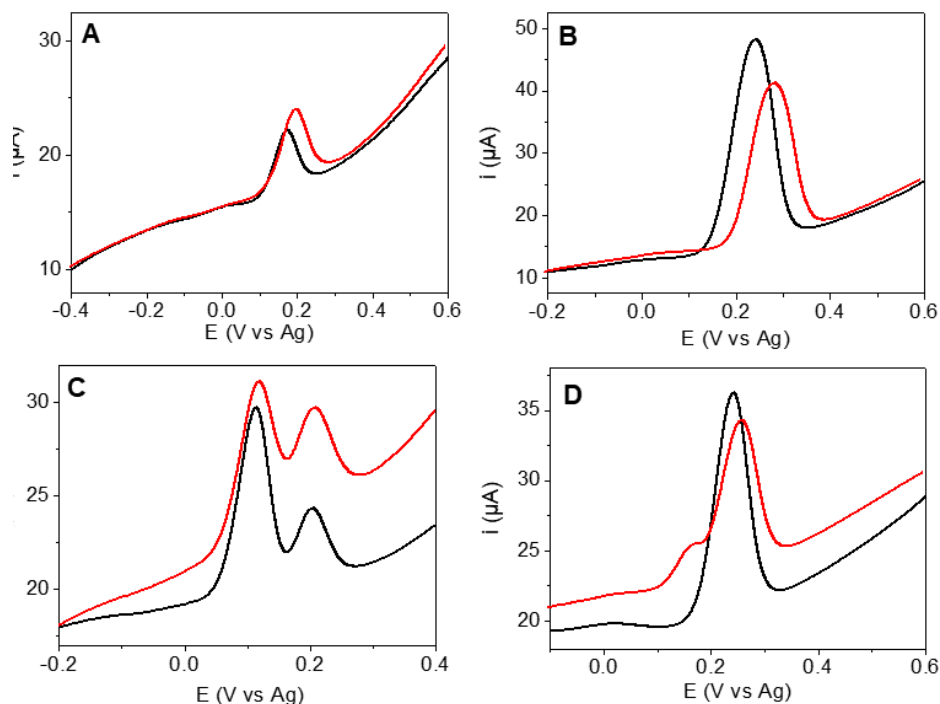
These observations indicate that the antioxidant activity of polyphenols can be modulated through the choice of the DES. The interactions between the DES and the polyphenols, depending on the nature of the DES might explain these observations. Notably, hydrogen bonding that plays a key role in the formation of DES,<sup>5</sup> is expected to influence the interaction between DES and polyphenols. Polyphenols groups are good hydrogen bond donors due to their hydroxyl groups and form bonds with good hydrogen bond acceptors.<sup>61</sup> A recent paper using a combination of methyl- $\beta$ -cyclodextrin and glycerol-based DES illustrates the importance of interactions between polyphenols and extracting media regarding their antioxidant activity.<sup>62</sup> The authors show that the cyclodextrin boosts the extraction yield of polyphenols while the antioxidant activity of the

extracts is not significantly higher due to specific interactions between cyclodextrin and polyphenols.<sup>62</sup>

On the whole, the possibility to vary the antioxidant activity of polyphenols with the DES composition could be of great interest to produce extracts with beneficial properties in which the extracting medium could serve as an active component. The extract could be directly employed in cosmetic or pharmaceutical uses by being part of the formulation.<sup>63</sup>

**Stability in BCA-water 30 %.** Solutions of catechin, epigallocatechin gallate, luteolin and rutin were stored for 10 months in a heat chamber at 30°C. DPV analyses were carried out in order to probe the stability of the polyphenols in BCA-water 30%. The DPV signals are fairly similar to those recorded originally with no significant variation of their redox potentials (< 30 mV, see Table S2), showing no degradation of the polyphenols after 10 months (Figure 7), with the exception of rutin (Figure 7D). The DPV signal for rutin displays a shoulder peak at about 0.17-0.19 V. This shoulder peak probably corresponds to the signal of quercetin formed upon the partial degradation of rutin into its aglycone counterpart in the acidic DES-based medium.

However, the DPV analyses demonstrate a remarkable stability of the polyphenols in the BCA-water 30 % DES, even under rather stringent conditions. This result is very promising for cosmetic or pharmaceutical formulation. Since the DES components are cosmetic-compatible, DES could be envisioned as functioning medium for the extraction and storage of bioactive phenolics, without the need of polyphenols isolation and recovery.



**Figure 7.** DPV signals of catechin (A), luteolin (B), epigallocatechin gallate (C) and rutin (D) in BCA-water 30 % before (black lines) and after (red lines) storage in a heat chamber at 30°C for 10 months.

## CONCLUSIONS

The direct electrochemistry of 9 phenolics, including 7 flavonoids, was investigated for the first time in 3 DES-based media using cyclic voltammetry and DPV. Well-defined signals were readily obtained at glassy carbon electrodes or using commercial SPE carbon system. Electrochemical analyses of phenolics in DES extracts can then constitute a potent alternative for the quantification of polyphenols contents, especially when considering that the routine Folin-Ciocalteu assay could be difficult to handle or even inaccurate in some DES media. Electrochemical techniques allow quick, simple and almost inexpensive analyses without requiring a complex sample preparation or the use of non- environmentally friendly reagents. This makes it possible the development of a

fully green process for polyphenols extractions that includes their quantification. A study with real extracts of herbs and medicinal plants using the DES-based media is currently in progress.

The antioxidant capacity of the polyphenols in the 3 DES-based media has been evaluated and compared through the values of their first redox peak potentials. The antioxidant capacity varies as a function of the DES composition, probably due to interactions between polyphenols and DES components. Thus, lower redox potentials are obtained in the acidic betaine-citric acid-water 30 % DES-based media than in the two neutral ethaline media, suggesting higher antioxidant activity of the flavonoids in betaine-citric acid-water 30 %. In addition, the polyphenols redox signal show a good to very good stability in betaine-citric acid-water 30 % after 10 months storage at 30 °C. These results open interesting perspectives in polyphenols extraction using DES where the extracting medium could serve as an active material in the formulation for cosmetic or pharmaceutical uses with beneficial effects for long-term storage and tuning of the antioxidant activity.

## **ASSOCIATED CONTENT**

Supporting Information. DPV of real thyme and green tea extracts and table of redox potentials of polyphenols.

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### **Author Contributions**

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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**SYNOPSIS (20 words)**

Electrochemistry show synergistic interactions between DES and polyphenols allowing modulation of antioxidant capacity: a route to green high-added value extracts.

### TOC Graphic

