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Response surface methodology and UPLC-QTOF-MS^E analysis of phenolic compounds from grapefruit (*Citrus × paradisi*) by-products as novel ingredients for new antioxidant packaging

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ABSTRACT

The present work reports an experimental study on the optimization of phenolic compounds extraction from *Citrus × paradisi* peels and the development of active packaging. Response surface methodology (RSM) was applied to investigate the effect of microwave-assisted extraction (MAE) for the recovery of total phenolic compounds (TPC). The TPC in the optimized extract were 31.10 mg gallic acid equivalent/100 g of dry weight (mg GAE/100 g dw) with strong antioxidant capacity. The bioactive compounds in the optimized extract were determined by ultrahigh performance liquid chromatography coupled to quadrupole time-of-flight with high energy mass spectrometry (UPLC-QTOF-MS^E). Forty-five compounds were detected and qualified. The optimized extract obtained by MAE was used as an active antioxidant in multilayer food packaging films. The multilayer low-density polyethylene (LDPE)/polyethylene terephthalate (PET) containing 10% of MAE optimized extract provided the most antioxidant power acting as a free radical scavenger.

1. Introduction

The citrus fruit is one of the most important crops worldwide as it is produced in over 100 nations. Its productivity was expected in 2016 at 132.4 million tons (Eryildiz, Lukitawesa, & Taherzadeh, 2020). Throughout the manufacturing of fruits, vast amounts of agri-food by-products are formed. These latter include precious substances, such as phenolic compounds, that can be transformed into added-value products (e.g., coronary heart disease). Numerous research is available regarding the high amount of phenolics and Citrus skin's antioxidant capacity (Jabbar et al., 2015). These constituents could be included within consumable and nutrient matters to enhance their antioxidant power (Marcos et al., 2014).

Bioactive molecules from citrus skins have been extracted by several researchers using different methods. The amount extracted and the valuable individual compounds can vary depending on the extraction factors (Oudjedi, Manso, Nerin, Hassissen, & Zaidi, 2019). This means that any extraction procedure requires careful optimization to get the highest efficiency.

The perfect extraction process requires high yields, be fast, easy to apply, be sustainable and must be non-deleterious. One of the methods that comply with these requirements is microwave-assisted extraction (MAE). It can be used without light and oxygen, with a low solvent volume and shorting the extraction time thanks to the high temperature or pressure in a static environment (Khan, Abert-Vian, Fabiano-Tixier, Dangles, & Chemat, 2010). Furthermore, a wide variety of solvents can be used in MAE since the method is a little reliant on the solvent connection (Zhang et al., 2013).

The present work deals with MAE application for the extraction of polyphenols from *Citrus × paradisi* peel. Response surface methodology (RSM) has been used as a practical means to assess the impacts of several variables and their connections on polyphenols extraction response.

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This investigation aimed to examine the impact of diverse variables on the effectiveness and recovery of total phenolics (TP) extracted from *Citrus × paradisi* peel using the MAE procedure. The extraction parameters assessed were microwave power, extracting period and liquid-to-matter fraction to optimize the TP amount. Beforehand, the bioactive molecules were identified and compared to those extracted by conventional extraction (CE). Once characterized, the extract was used as an antioxidant agent in new active packaging. For this purpose, different concentrations of the optimized MAE extract were incorporated into a multilayer plastic film, and their antioxidant activity was evaluated at a laboratory scale. This active packaging represents the main novelty of this research.

2. Materials and methods

2.1. Material

DPPH (2,2-Diphenyl-1-picrylhydrazyl, CAS 1898-66-4), ABTS™ (2,2′-Azino-bis (3–119 ethylbenzothiazoline-6-sulfonic acid) diammonium salt (CAS 30931-67-0), β-carotene (CAS 7235-40-7), gallic acid (CAS 149-91-7), sodium salicylate (CAS 54-21-7), sodium acetate (CAS 127-09-3), acetic acid (≥99.7%, CAS 64-19-7), formic acid (CAS 64-18-6) were supplied by Sigma-Aldrich (Germany). Ethanol absolute pure (CAS 64-17-5) and methanol (LC-MS, CAS 67-56-1) were from Pan Reac Appli Chem (Barcelona, Spain). Ultrapure water was from Wasser lab Ultramatic GR system, Barbatáin.

2.2. Samples

All samples of *Citrus × paradisi* were purchased in the region of Bejaia in October 2017. The identification of the grapefruit species was carried out by the experimental department of the ITAF (Technical Institute of the Arboriculture Fruit and Vine) of Boufarik, Blida (Algeria). The fruits were cleaned up using distilled water and then peeled. The obtained by-products were dehydrated in freeze drier apparatus (ALPHA 1–2 LD plus) at - 65 °C and 0.044 mbar. After that were powdered and sieved using a sieve whose diameter was ≤250 μm. The powder's water activity (aw) was determined by a Hygro Palm AW1 portable water activity meter (Rotronic, Bassersdorf, Switzerland); the result was 0.15 ± 0.02 at 20.6 °C.

2.3. Extraction procedure

The main characteristics of the used apparatus (Maxipower model: MaxMo23S, S/NSC1106600624, Algeria) were as follows: cavity dimensions of 281 mm (H) × 483 mm (W) × 387 m (D); a frequency of 2.45 GHz to determine the period and power ranged from 100 to 900 W.

The extraction procedure consists of putting 1 g of the sample with the solvent in a 250 mL volumetric flask, and then the mixture was irradiated. According to the assay, different solvents, irradiation periods, microwave powers and liquid-to-solid ratios were adopted (Table 1).

After that, the suspension was passed through a filter, and the solvent was evaporated. The freeze-dehydrated extracts were stocked up in glass flasks at 4 °C until further use.

2.4. Experimental design

Box–Behnken experimental Design (BBD) adopted in this work concentrated on the impacts of four variables that were as follows: A: ethanol concentration (40–80%); B: irradiation power (100, 300, 500, 700 and 900 W); C: extraction time (30, 60, 90 et 120 s); D: liquid-to-matter proportion (1:10, 1:30, 1:50, 1:70, 1:90, *w/v*). The BBD matrix employed for optimization and the level of each variable are shown in Table 2. The total phenolic content of every assay and the TPC for single variables at each level was determined and employed to assess the effectiveness and to optimize the experimental conditions.

2.5. Determination of differences between MAE and traditional methods

For MAE: 1 g of sample powder was extracted following the optimized conditions: ethanol concentration 40%, extraction time 30 s, irradiation power 300 W, and the solid-to-solvent ratio of 1:70 (g/mL). In the maceration procedure, 1 g of grind sample and 70 mL of ethanol 40% (*v/v*) were mixed and placed in a water bath (mod.WNB22 Memmert, Germany) for 2 h; the speed was 110 strokes/min and the temperature 60 °C (Spigno, Tramelli, & De Faveri, 2007).

2.6. Quantification of total phenolics and non-volatile compounds by UPLC-QTOF-MS^E

The method reported by Škerget et al. (2005) was applied to get the TPC values. The data were expressed as grams of gallic acid equivalent

Table 1
Results of single-factor experiments for MAE (Microwave-Assisted Extraction) (part a), the coded values and corresponding actual values of the optimization parameters used the response surface analysis (part b).

Part (a) Solvent type	TPC	Ethanol [C] (%, *v/v*)	TPC	Irradiation time (s)	TPC	Microwave power (W)	TPC	Solvent-to-solid ratio (mL/g)	TPC
Water	19.50 ± 0.42^c	**20**	20.79 ± 1.96^c	**30**	25.59 ± 0.71^{b,c}	**100**	21.99 ± 1.35^c	**10**	15.69 ± 0.45^c
50% EtOH	23.00 ± 0.40^a	**40**	21.76 ± 0.29^c	**60**	26.98 ± 0.89^a	**300**	25.10 ± 0.14^b	**30**	26.06 ± 0.88^b
50% MeOH	21.25 ± 0.18^b	**60**	26.98 ± 0.89^a	**90**	26.53 ± 0.32^{a,b}	**500**	26.98 ± 0.89^a	**50**	55.27 ± 0.56^a
50% acetone	20.90 ± 0.10^b	**80**	24.54 ± 0.58^b	**120**	24.86 ± 0.43^c	**700**	24.52 ± 0.65^b	**70**	32.24 ± 0.62^b
		100	21.99 ± 0.19^c	**150**	23.08 ± 0.52^d	**900**	24.81 ± 0.13^b	**90**	29.62 ± 0.39^b
				180	23.05 ± 0.25^d				

Part (b)

Code	Ethanol concentration (%)	Microwave power (W)	Irradiation time (s)	Ratio (mL/g)
−	40	300	30	30
0	60	500	60	50
+	80	700	90	70

EtOH: Ethanol, MeOH: methanol, results are reported as means ± SD. Same letters in the same column refers to means not statistically different according to ANOVA and Tukey's test ($P > 0.05$). TPC, total phenols content referred to dry weight (dw) of C.× paradisi peelsexpressed in GAE, Gallic Acid Equivalents.

Table 2
Analysis of variance for the TPC (Total Phenolic Compounds) on factors effect using the BBD (Box–Behnken experimental Design) of the response surface.

Term	Sum of Squares	t Ratio	Prob > F	F Ratio	DF	Estimate	Std Error
Intercept	77.75395	52.96	<.0001	191.9706	1	19.461218	0.367437
Linear							
X_1-Solvent	3.74594	−13.86	0.0103	9.2485	1	−2.545485	0.183719
X_2-Power	0.00576	−3.04	0.9070	0.0142	1	−0.558714	0.183719
X_3- Time	21.71684	0.12	<.0001	53.6178	1	0.0219164	0.183719
X_4- Ratio	5.01040	7.32	0.0042	12.3704	1	1.3452646	0.183719
Interaction							
X_1X_2	4.00501	−3.52	0.0085	9.8882	1	−1.119197	0.31821
X_1X_3	7.00770	−3.14	0.0013	17.3017	1	−1.000626	0.31821
X_2X_3	23.01883	4.16	<.0001	56.8323	1	1.323603	0.31821
X_1X_4	0.85362	−7.54	0.1722	2.1076	1	−2.398897	0.31821
X_2X_4	6.36310	−1.45	0.0019	15.7102	1	−0.461959	0.31821
X_3X_4	111.20403	−3.96	<.0001	274.5572	1	−1.261259	0.31821
Quadratic							
X_1^2	1.54199	16.57	0.0748	3.8071	1	4.5662628	0.275578
X_2^2	0.11279	−1.95	0.6073	0.2785	1	−0.537701	0.275578
X_3^2	0.41498	0.53	0.3314	1.0246	1	0.145426	0.275578
X_4^2	77.75395	−1.01		191.9706	1	−0.278944	0.275578
Lack of Fit	3.8654797		0.6818	0.7771	10		
Pure Error	0.9948863			0.6818	2		
Total Error	4.8603661			0.9967	12		
C.Total	304.02373				26		
R^2	0.984013						
R^2 Adj	0.965362						
RMSE	0.6364						

per gram of extract (g GAE/g extract).

The bioactive non-volatile compounds of MAE and CE extracts were analyzed by UPLC-QTOF-MS^E. The extracts were diluted 100 times with ethanol 40%. The samples were previously filtered using a syringe filter (nylon, 0.22 μm from Millipore, Sigma-Aldrich, Madrid, Spain) and injected. Chromatographic separation and identification were performed using XEVO^{TM}G2 QT of MS from Waters (Milford, MA, USA). The column applied was: Acquity UPLC BEH C18; 2.1 × 100 mm and 1.7 μm particle size (Waters). Electrospray ionization (ESI) was carried out in positive and negative mode. Mass was corrected during acquisition using Lock Spray™.

The same conditions reported were adopted. Mass Lynx software was used for data collection and analysis, and all samples were analyzed in triplicate.

2.7. Assessment of antioxidant capacity

DPPH$^{\bullet}$ scavenging power was evaluated, as stated in literature (Sánchez-Moreno, Larrauri, & Saura-Calixto, 1998). The data were expressed as the inhibition percentage of free radical by the sample and calculated as indicates in equation (1).

$$\text{DPPH}\ (\%) = ((A_{control} - A_{sample})/A_{control}) \times 100 \quad (1)$$

Regarding reducing power, the procedure given in the literature (Oyaizu, 1986) was followed. The measurement of the radical cations ABTS$^{\bullet+}$ scavenged by the antioxidants of grapefruit was performed using the technique of Re et al. (1999). For the three assays, the IC_{50} values (mg/mL) were calculated.

The extracts were also tested by the β-carotene/linoleic acid bleaching method following the procedure described by Prakash, Mishra, Kedia, & Dubey, 2014. The antioxidant activity was computed as indicates equation (2).

$$I\ (\%) = (A_t/A_0) \times 100 \quad (2)$$

Where A_0 (starting absorbance) and A_t (after 2 h) were determined at 470 nm.

2.8. Preparation of packaging with antioxidants

A multilayer film of low-density polyethylene (LDPE) and polyethylene terephthalate (PET) was built using an aqueous dispersion adhesive containing the optimized extract of grapefruit peel obtained MAE. Three different concentrations of MAE extract 2%, 5% and 10% (*w/w*) in the adhesive were tested, while the extract obtained by CE was added at 5% (*w/w*).

This adhesive formula (with or without extract) was spread on the LDPE sheet using the coating machine with a bar of thickness N° 1, allowing homogeneously to extend the active adhesive on the film. After air-drying of the adhesive-extract formula, the PET layer sheet was glued to the LDPE. Blank samples were prepared using the same procedure but without active extract in the adhesive. Thermostable bags with a dimension of 15 cm× 15 cm were prepared from the multilayer sheets to evaluate the material's antioxidant activity, following the procedure developed by Pezo, Salafranca, and Nerín (2006).

2.9. Statistical analysis

Each trial was carried out in triplicate. Statistical software (version 5.5, StatSoft, Inc., Tulsa, USA) was employed to set up a mathematical model. Analysis of variance was carried out to point out if the differences were statistically significant.

3. Results and discussion

3.1. Microwave-assisted extraction

The selection of the extraction solvent is essential since it plays a critical role in the amount and type of phenolic compounds extracted (Spigno et al., 2007). Binary solvent systems are usually more efficient and favourable in extracting phenolic compounds from plants than pure solvent systems (Turkmen, Sari, & Velioglu, 2006). So, to choose the appropriate solvent, four solvent systems were tested: water, methanol, ethanol, and acetone, all of them diluted to 50% (*v/v*) with water.

According to the results obtained (Table 1), ethanol 50% (*v/v*) provided the highest content of TP (23.00 ± 0.40 mg GAE/g dw) compared to the others. Galan et al. (2017) described that ethanol attracts and changes microwaves to thermal energy, hence facilitating the

fast-breaking of the cellular wall and increasing the extraction. This performance is attributed to a higher dissipation factor (tan δ) than other solvents, which is 0.941, and a dielectric constant of 24.3 (Bonnaillie, Salacs, Vassiliova, & Saykova, 2012). Thus, ethanol was selected in this study as the variable to be tested in the optimization design.

3.1.1. Preliminary study

Preliminary studies allowed the determination of lower and upper levels of experimental design variables used to select an appropriate interval for TPC extraction for each independent variable.

The maximum TPC yield (26.98 ± 0.89 mg GAE/g dw) using MAE was achieved using ethanol 60% (*v/v*), then this value was used for the rest of the experiments. However, for statistical analysis (Table 1), a range between 40 and 80% was chosen for the RSM assays.

The irradiation period significantly impacted the TP amount, which increases with the extraction time ranging from 30 to 90 s, from which a decrease was observed (Table 3). This is probably due to the degradation of phenolic compounds caused by microwave irradiation at extended extraction times (Alara, Abdurahman, & Olalere, 2018). According to the obtained values, 60 s was chosen for the subsequent single-factor tests, whilst series 30–90 s were chosen for the RSM assays.

The TP content increased by rising microwave power from 100 to 500 W; after that, it slightly decreased at higher power, without significant difference ($P < 0.05$) between 700 and 900 W. Excessive microwave power can lead to the degradation of the bioactive compounds (Dahmoune et al., 2013). Thus, microwave power was set at 500 W for preliminary testing, while the 300–700 W range was used for the RSM study.

According to Prakash Maran, Sivakumar, Thirugnanasambandham, and Sridhar (2013), a higher solvent ratio to raw material provides a better gradient through the matter's dispersion of the liquid. The increase of the solvent/solid rate facilitates the contact area between the material and the solvent. Nevertheless, with an increase in the liquid/-solid ratio, a decrease in yield was observed at ratios of 70/1 and 90/1 mL/g, as expected because of the dilution factor. This fact agrees with the results of Shirsath et al. (2017). The L/S ratio was set at 50/1 mL/g for preliminary testing, while the 10/1 to 50/1 mL/g range was used for the RSM study.

3.1.2. Experimental design

Several parameters, such as solvent concentration, extraction time, temperature, extraction power and solvent–matter ratio, impact the MAE efficiency. To obtain the optimum extraction conditions for MAE of *C.× paradise*, the experimental design of a 4-factor (with a total of 27 experiments) was applied to show the most substantial factors influencing the response studied (TPC). The four factors under consideration were ethanol concentration (X1), microwave power (X2), irradiation period (X3) and liquid-to-matter fraction (X4).

The yield of TPC and the factors studied are represented in the mathematical model by a second-order polynomial equation according to equation (3).

$$\mathrm{YTPC} = 19.46 - 2.53X1 - 0.55X2 + 0.02X3 + 1.34X4\ 4.56X12 - 0.53X22 + 0.14X32 - 0.27X42 - 1.11X1X2 - 1.00\ X1X3 + 1.32X2X3 - 2.39X1X4 - 0.46X2X4 - 1.26X3X4 \quad (3)$$

The independent variables have a linear impact on TPC (Y) in the testing array in MAE. The TPC was influenced more significantly ($P < 0.001$) by the first variable (X_1) followed by the microwave power (X2) with the probability of 0.0103. However, the impact is not significant for other factors. Concerning the quadratic effects, only the factor $X1^2$ (solvent * solvent) significantly affected the TPC compared to other quadratic effects such as $X2^2$ (power * power), $X3^2$ (time * time) and $X4^2$ (ratio * ratio), that have no significant effects with probabilities of 0.0748, 0.6073 and 0.3314, respectively.

The effects of the independent variables and the mutual interaction of the TPC extraction efficiency can also be seen in the three dimensions response surface curves shown in Fig. 1. It is noted that only the interaction of ethanol concentration and solid ratio (X_1X_4) was highly significant at $p < 0.0001$. Besides, ethanol concentration and power (X1X2), ethanol concentration and period (X1X3), power and time (X2X3), and time and ratio (X3X4) exhibited significant interaction at values of p 0.0042, 0.0085, 0.0013 and 0.0019, respectively. However, the interaction (X2 X4) was not significant.

Table 3
Box–Behnken Design with the observed responses and predicted values for TPC (Total Phenolic Compounds) using MAE (Microwave-Assisted Extraction).

Run	X_1-% Ethanol concentration (*v/v*)	X_2- Power (W)	X_3- Time (s)	X_4- Ratio (mL/g)	TPC yield (mg GAE/g dw)	
					Experimental	Predicted
1	60	500	60	50	19.47	20.12
2	40	500	60	30	22.52	21.67
3	60	700	60	30	17.23	16.91
4	60	300	60	70	20.90	21.21
5	60	700	30	50	16.66	18.28
6	60	700	60	70	19.68	18.84
7	80	700	60	50	19.04	18.93
8	40	300	60	50	25.90	25.47
9	60	700	90	50	20.04	19.81
10	80	500	90	50	20.07	20.52
11	60	500	90	30	19.86	18.93
12	60	500	30	70	21.52	21.91
13	80	500	60	70	20.04	19.44
14	60	500	90	70	19.42	19.76
15	60	300	60	30	16.60	17.43
16	60	300	30	50	20.60	21.38
17	60	500	30	30	16.91	17.03
18	80	500	30	50	23.10	22.64
19	60	500	60	50	18.74	20.12
20	60	300	90	50	18.69	19.61
21	60	500	60	50	20.15	20.12
22	80	300	60	50	23.04	22.62
23	40	700	60	50	26.38	26.26
24	40	500	90	50	27.16	27.61
25	40	500	30	50	26.18	25.73
26	80	500	60	30	22.23	21.38
27	40	500	60	70	29.93	29.32

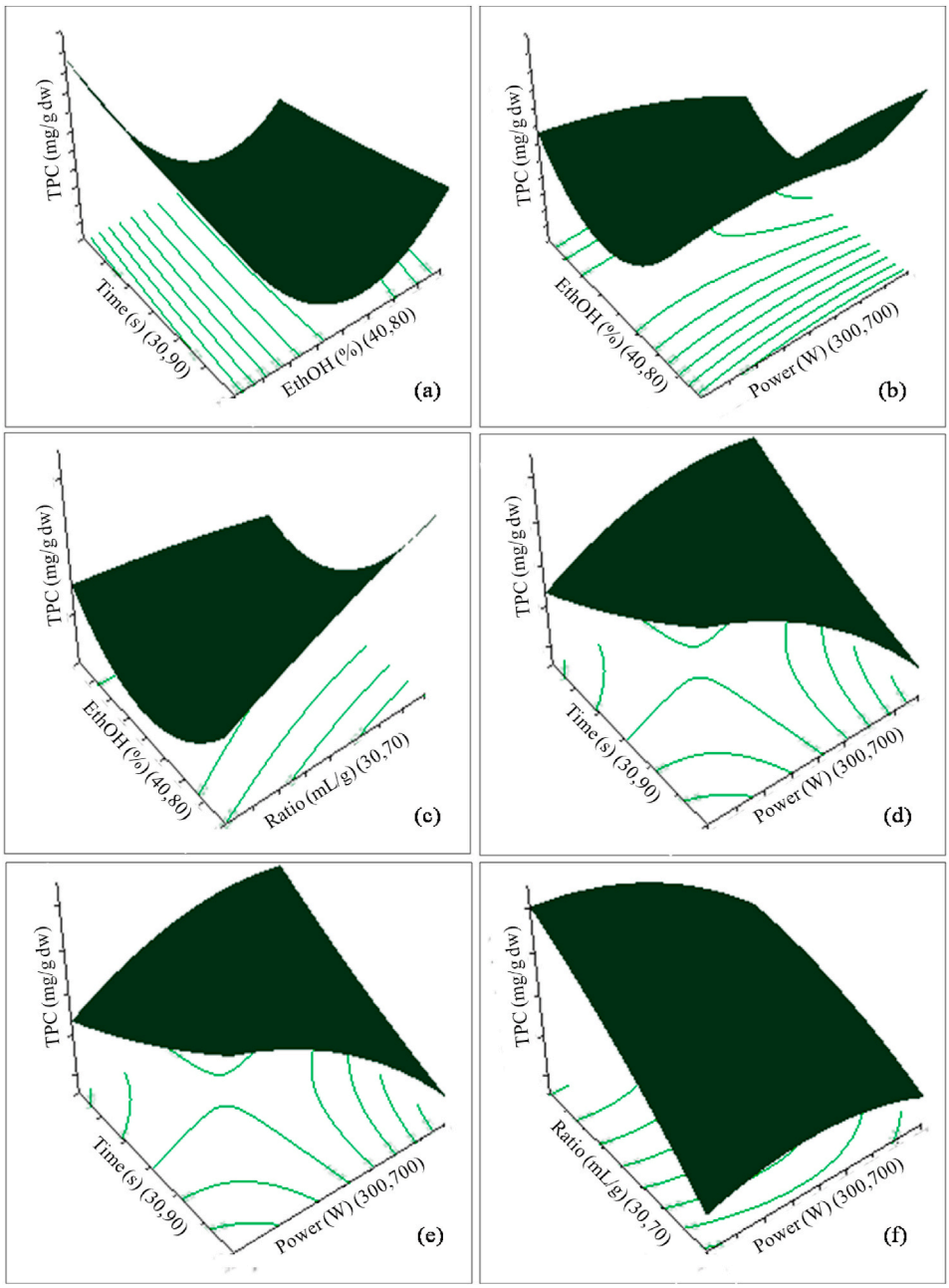

Fig. 1. Response surface analysis for the total phenolic compounds (TPC) with MAE (Microwave-Assisted Extraction) with respect to: (a) ethanol concentration and irradiation time; (b) ethanol concentration and power; (c) ethanol concentration and solvent-to-solid ratio; (d) extraction time and power; (e) extraction time and solvent-to-solid ratio; and (f) power and solvent-to-solid ratio.

3.1.3. Validation of the model

The results of the effect of the factors on TPC are represented by the regression coefficients in Table 2. The recorded results showed that the model represents adequately the relationship between the selected parameters and the response. This analysis showed that the model is very significant ($P < 0.0001$) with a regression coefficient (R^2) of 0.97. Besides, the value of the coefficient of adjustment ($Radj^2$) is 0.95.

3.1.4. Optimal conditions

The optimum conditions for the extraction of polyphenols from *Citrus × paradisi* fruit peels by microwave were obtained using the regression equations of the response surface methodology. The results obtained were as follows: 40% ethanol, 300 W microwave power, 30 s irradiation period and a solvent-to-matter fraction of 70 mL/g.

Under these optimal conditions, the experimental value was 29.19 ± 0.59 mg/g of TPC, close to the value predicted by the software, which was 31.10 ± 2.11 mg/g. This value is included in the interval predicted by the latter 28.99–33.21 mg/g, confirming the chosen model's validity. The high correlation between the measured and expected results confirmed that the response of the regression model was sufficient to repeat the predictable optimization (Zhang et al., 2013).

3.2. Qualitative analysis of bioactive non-volatile compounds by UPLC-QTOF-MS^E

Separation and identification of bioactive non-volatile compounds from grapefruit peel extracts were performed using UPLC-QTOF-MS^E. MS high energy (MS^E) is a novel technique in which parallel collection of ion fragments from low and high-energy acquisitions occurs. As a result, the exact mass of the parent ion and the fragment ions of daughters are

obtained in the same way for each analyte. Fig. 2 shows an example of chromatograms with marked retention times of peaks obtained in positive and negative modes. Good chromatographic resolution and sensitivity were achieved. The elution time was chosen as 10 min as there wasn't any analyte eluted after this time. The presented chromatogram of first function was used for qualitative analysis of chemical determined in a process of elemental composition acquired from spectrum of each peak. Subsequently chromatogram of second function was used to match possible molecule mass fragments with the spectrum of analytes.

The profile of bioactive non-volatile compounds was determined in positive electrospray ionization mode (ESI^+). Positive ion formation is encouraged by low pH and during negative electrospray ionization mode (ESI^-), deprotonated molecules can be observed. Table 4 is correlated with Fig. 2 and lists in detail the detected non-volatile compounds numbered according to their retention time and chemical class, molecular formula, *m/z* and formed adducts. Forty-five different non-volatile compounds were detected and qualified in total. These are mainly coumarins such as 4-hydroxycoumarin, 7-hydroxycoumarin and haploperoside and flavonoids (naringin, naringenin, luteolin 7-*O*- rutinoside, nobiletin, penta-*O*-methylquercitin and 3, 5, 6, 7, 8, 3′, 4′-heptamethoxyflavone). Coumarins present in citrus are connected with pathogens defense of fruits. The second group of detected compounds are flavonoids that are under interest of researchers. They are secondary plant metabolites showing interesting antioxidant properties, strong radical scavenging activity and also having wide health benefits. Among detected flavonoids there were luteolin 7-*O*- rutinoside, naringin, naringenin compounds and rosavin with excellent antioxidants capacities. Moreover, aromatic compounds, such as different isomers of 4-ethyl-7-methyl-5-(2-oxopropoxy)-2H-chromen-2-one, eluted between 4.0 and 5.5 min in positive mode, can also contribute to antioxidant properties of *Citrus × paradisi* peels. All detected and mentioned compounds can be significant contributors to chemical properties of analyzed samples. To our knowledge, there is no data in the literature about non-volatile compounds from Algerian grapefruit (*Citrus × paradisi*) peel extract. Furthermore, the number of studies is minimal on the peel composition of other grapefruits species (Xi, Fang, Zhao, Jiao, & Zhou, 2014). Among the compounds identified in the juices and citrus peel extracts, naringin, naringenin, nobiletin, eriocitrin, narirutin, hesperidin, rhoifolin, diosmin, and citrusoside A (Youkwan, Sutthivaiyakit, & Sutthivaiyakit, 2010). Lü, Zhang, Wu, Zhou, and Yu (2016) and Xi et al. (2014) found in local Chinese grapefruit other compounds of the same family and some identical to those found in this study, such as naringenin, hesperetin, eriocitrin, nobiletin and diosmin.

By studying orange peel phenolic compounds, Khan et al. (2010),

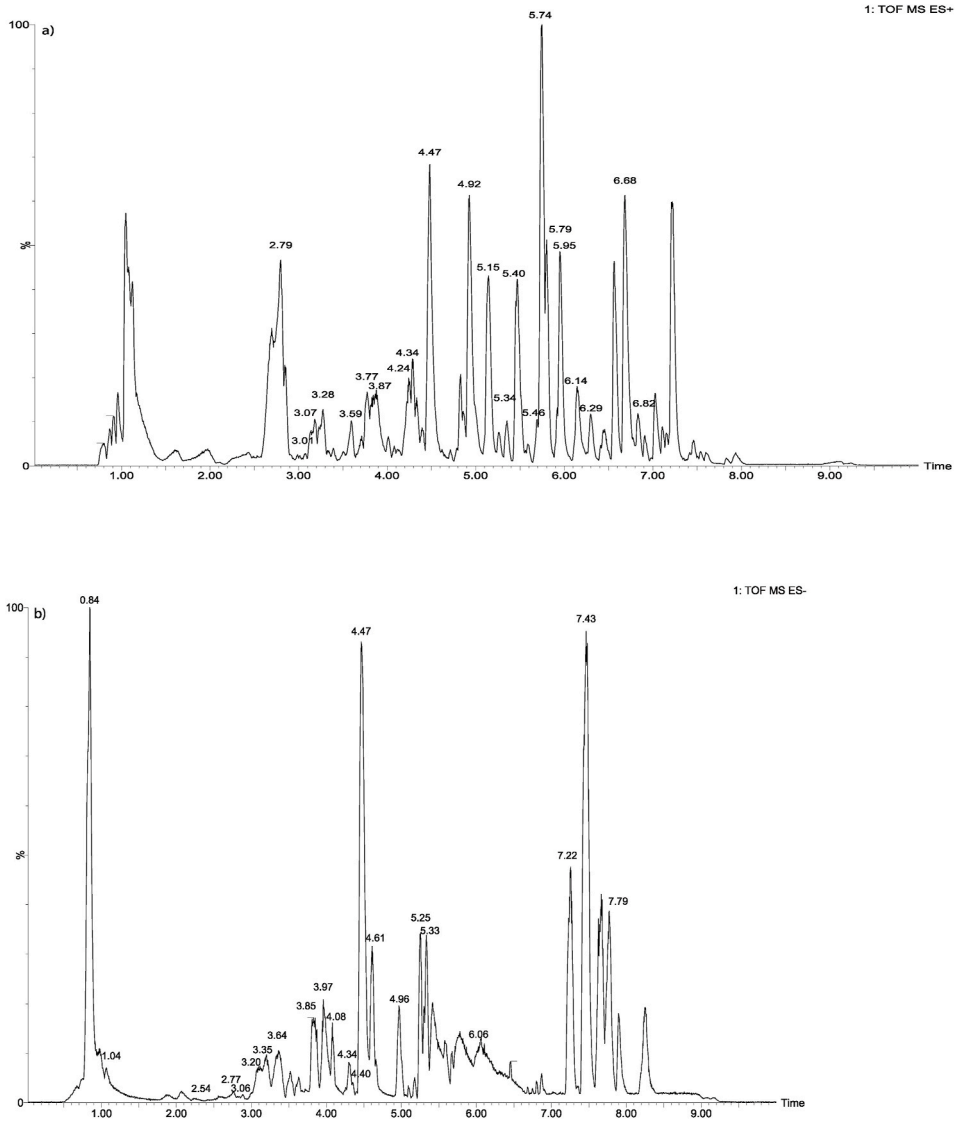

Fig. 2. Example of obtained chromatograms for CE sample by UPLC-QTOF-MS^E (Ultrahigh Performance Liquid Chromatography coupled to Quadrupole Time-Of-Flight with high Energy Mass Spectrometry) in a) positive mode; b) in negative mode.

Table 4
Results of qualitative analysis in grapefruit peel extracts by UPLC-QTOF-MS^E (Ultrahigh Performance Liquid Chromatography coupled to Quadrupole Time-Of-Flight with high Energy Mass Spectrometry) in positive and negative mode. Symbol "●" means that detected compound is present in the sample.

No	tR (min)	Compound	Class	Molecular formula	CAS	Adduct	m/z	Sample	
								CE	MAE
Positive mode									
1	2.79	k-strophanthidin	flavonoid	$C_{23}H_{32}O_6$	000066-28-4	$[M+Na]^+$	427.2102	●	●
2	3.01	haploperoside	coumarins	$C_{22}H_{28}O_{13}$	097938-29-9	$[M+H]^+$	501.1617	●	●
3	3.07	(6S,9S)-roseoside	flavonoid	$C_{19}H_{30}O_8$	185414-25-9	$[M+Na]^+$	409.1838	●	●
4	3.28	luteolin 7-*O*- rutinoside	flavonoid	$C_{27}H_{30}O_{15}$	020633-84-5	$[M+H]^+$	595.1666	●	●
5	3.48	benzyl 2-*O*-acetyl-4-*O*-(3-*O*-allyl-β-D-galactopyranosyl)-β-D-glucopyranoside	flavonoid	$C_{24}H_{34}O_{12}$	Not found	$[M+Na]^+$	537.1973	●	●
6	3.59	2-(4-isobutoxyphenyl) succinic acid	carboxylic acid	$C_{14}H_{18}O_5$	Not found	$[M+H]^+$	267.1236	●	●
7	3.77	naringin	flavonoid	$C_{27}H_{32}O_{14}$	010236-47-2	$[M+H]^+$	581.1875	●	●
8	3.87	naringenin	flavonoid	$C_{15}H_{12}O_5$	000480-41-1	$[M+H]^+$	273.0772	●	●
9	4.24	4-ethyl-7-methyl-5-(2-oxopropoxy)-2H-chromen-2-one (isomer 1)	aromatic	$C_{15}H_{16}O_4$	314742-55-7	$[M+H]^+$	261.1132	●	●
10	4.34	4-ethyl-7-methyl-5-(2-oxopropoxy)-2H-chromen-2-one (isomer 2)	aromatic	$C_{15}H_{16}O_4$	314742-55-7	$[M+H]^+$	261.1132	●	●
11	4.47	4-ethyl-7-methyl-5-(2-oxopropoxy)-2H-chromen-2-one (isomer 3)	aromatic	$C_{15}H_{16}O_4$	314742-55-7	$[M+H]^+$	261.1132	●	●
12	4.92	4-ethyl-7-methyl-5-(2-oxopropoxy)-2H-chromen-2-one (isomer 4)	aromatic	$C_{15}H_{16}O_4$	314742-55-7	$[M+H]^+$	261.1132	●	●
13	5.15	[(3-hexyl-4,8-dimethyl-2-oxo-2H-chromen-7-yl)oxy]acetic acid	aromatic	$C_{19}H_{24}O_5$	438030-13-8	$[M+Na]^+$	355.1510	●	●
14	5.34	2,3,6-trimethyl-L-tyrosyl-D-alanyl-L-phenylalanylglycyl-L-valyl-L-valylglycinamide	peptide amide	$C_{38}H_{62}O_{16}$	Not found	$[M+Na]^+$	753.4303	●	●
15	5.40	citrusoside A	liposaccharide	$C_{21}H_{36}O_7$	Not found	$[M+Na]^+$	423.2328	●	●
16	5.46	ethyl 3-{4-methyl-2-oxo-7-[(2-oxocyclohexyl)oxy]-2H-chromen-3-yl}propanoate	aromatic	$C_{21}H_{24}O_6$	Not found	$[M+Na]^+$	395.1460	●	●
17	5.74	nobiletin	flavonoid	$C_{21}H_{22}O_8$	000478-01-3	$[M+H]^+$	403.1428	●	●
18	5.79	3,5,6,7,8,3′,4′- heptamethoxyflavone	flavonoid	$C_{22}H_{24}O_9$	001178-24-1	$[M+H]^+$	433.1516	●	●
19	5.95	penta-*O*-methylquercitin	flavonoid	$C_{20}H_{20}O_7$	001247-97-8	$[M+H]^+$	373.1299	●	●
20	6.14	(8S,16Z)-4-(2,3-dihydro-1,4-benzodioxin-6-yl)-5-methoxy-8-methyl-4,8,9,10,11,13,14,15-octahydro-2H,6H-oxacyclotetradecino[3,4-g]chromene-2,6,12(3H)-trione	flavonoid	$C_{30}H_{32}O_8$	Not found	$[M+Na]^+$	543.2007	●	●
21	6.29	scutebata A	terpenoid	$C_{36}H_{40}O_{10}$	1207181-57-4	$[M+Na]^+$	655.2524	●	●
22	6.68	bis[2-(4-biphenylyl)-2-oxoethyl] dodecanedioate	ester	$C_{40}H_{42}O_6$	Not found	$[M+H]^+$	619.3062	●	●
23	6.82	2,2′-dimethoxy-3,3′,4,4′-tetrabenzyloxy-6,6′-bis(hydroxymethyl) biphenyl	aromatic	$C_{44}H_{42}O_8$	Not found	$[M+H]^+$	699.2935	●	●
Negative mode									
1	0.84	quinic acidisomer 1	carboxylic acid	$C_7H_{12}O_6$	000077-95-2	$[M-H]^-$	191.0667	●	●
2	1.04	quinic acid isomer 2	carboxylic acid	$C_7H_{12}O_6$	000077-95-2	$[M-H]^-$	191.0667	●	●
3	2.56	4-hydroxycoumarin	coumarin	$C_9H_6O_3$	001076-38-6	$[M-H]^-$	161.0229	●	●
4	2.77	7-hydroxycoumarin	coumarin	$C_9H_6O_3$	000093-35-6	$[M-H]^-$	161.0226	●	●
5	3.06	rosavin isomer 1	flavonoid	$C_{20}H_{28}O_{10}$	084954-92-7	$[M-H]^-$	427.1591	●	●
6	3.20	rosavin isomer 2	flavonoid	$C_{20}H_{28}O_{10}$	084954-92-7	$[M-H]^-$	427.1610	●	●
7	3.35	pectolinarigenin 7-rutinoside	flavonoid	$C_{29}H_{34}O_{15}$	028978-02-1	$[M-H]^-$	621.1826	●	●
8	3.64	eriocitrin	flavonoid	$C_{27}H_{32}O_{15}$	013463-28-0	$[M-H]^-$	595.1665	●	●
9	3.85	narirutin isomer 1	flavonoid	$C_{27}H_{32}O_{14}$	014259-46-2	$[M-H]^-$	579.1715	●	●
10	3.97	narirutin isomer 2	flavonoid	$C_{27}H_{32}O_{14}$	014259-46-2	$[M-H]^-$	579.1725	●	●
11	4.08	hesperidin	flavonoid	$C_{28}H_{34}O_{15}$	000520-26-3	$[M-H]^-$	609.1807	●	●

(*continued on next page*)

Table 4 (*continued*)

No	tR (min)	Compound	Class	Molecular formula	CAS	Adduct	m/z	Sample	
								CE	MAE
Positive mode									
12	4.34	rhoifolin	flavonoid	$C_{27}H_{30}O_{14}$	017306-46-6	$[M-H]^-$	577.1560	●	●
13	4.40	diosmin	flavonoid	$C_{28}H_{32}O_{15}$	000520-27-4	$[M-H]^-$	607.1659	●	●
14	4.47	xanthotoxol	coumarin	$C_{11}H_6O_4$	002009-24-7	$[M-H]^-$	201.0195	●	●
15	4.61	plantamajoside	polyphenol	$C_{29}H_{36}O_{16}$	104777-68-6	$[M-H]^-$	639.1927	●	●
16	4.96	L-valyl-L-leucyl-L-prolyl-L-alanyl-L-alanyl-L-proline	peptide	$C_{27}H_{46}N_6O_7$	503844-12-0	$[M-H]^-$	565.3350	●	●
17	5.25	ethyl 3-{4-methyl-2-oxo-7-[(2-oxocyclohexyl)oxy]-2H-chromen-3-yl}propanoate isomer 1	aromatic	$C_{21}H_{24}O_6$	5614-82-4	$[M-H]^-$	371.1476	●	●
18	5.33	ethyl 3-{4-methyl-2-oxo-7-[(2-oxocyclohexyl)oxy]-2H-chromen-3-yl}propanoate isomer 2	aromatic	$C_{21}H_{24}O_6$	5614-82-4	$[M-H]^-$	371.1476	●	●
19	5.42	2,5-di-*tert*-butyl-3-hydroxy-6-methoxy-1,4-benzoquinone	aromatic	$C_{15}H_{22}O_4$	Not found	$[M-H]^-$	265.1465	●	●
20	7.22	elaidolinolenic acid	fatty acid	$C_{18}H_{30}O_2$	028290-79-1	$[M-H]^-$	277.2183	●	●
21	7.43	(9E,12E)-9,12-octadecadienoic acid	fatty acid	$C_{18}H_{32}O_2$	002420-55-5	$[M-H]^-$	279.2327	●	●
22	7.79	oleic acid	fatty acid	$C_{18}H_{34}O_2$	000112-80-1	$[M-H]^-$	281.280	●	●

using HPLC-DAD, quantified hesperidin and naringin with the content of 205.20 and 70.30 mg/100 g fw, respectively. Similarly, *Citrus × sinensis* was characterized by the presence of high quantities of hesperidin and naringenin (Safdar et al., 2017) and 3, 5, 6, 7, 8, 30, 40- heptamethoxyflavone, nobiletin were found by Duan et al. (2017) in *Citrus reticulata* 'Chachi' peels.

3.3. Comparative study between the two tested extraction methods

The results of the TPC and the antioxidant activities obtained by MAE in optimal conditions for the extraction of total phenolics were compared to those obtained by the CE.

The CE showed significantly lower TPC (26.75 ± 1.15 mg GAE/g dw) than MAE (31.10 ± 2.11 mg GAE/g dw). Our results are similar to those reported by several authors (Hemwimon, Pavasant, & Shotipruk, 2007; Zhang, Yang, & Liu, 2008) that showed that the MAE procedure is more efficient in comparison to CE. This can be explained by the extraction mechanism involved in MAE. Increasing temperature and pressure can cause rapid migration of target compounds. This performance can be attributed to the thermal effect that enhances the dipolar rotation of the solvent, thus increasing the solubility of the compounds (Hemwimon et al., 2007).

3.4. Antioxidant activity of the extracts

According to the results shown in Table 5, MAE's extract had a high antioxidant activity compared to the one resulted from the conventional method (CE) in all the used tests. In DPPH scavenging capacity, the extract obtained from MAE showed significantly lower IC_{50} (12.81 ± 0.14 mg/mL) than the CE method (20.89 ± 0.41 mg/mL). The same trend was noticed in the ABTS assay, where the extract from MAE also provided significantly lower IC_{50} (1.90 ± 0.02 mg/mL) compared to CE (2.02 ± 0.01 mg/mL). Still, it showed poor scavenging ability on ABTS•+ radicals compared to other plant materials reported in the literature (Dudonné, Vitrac, Coutiére, Woillez, & Mérillon, 2009). Besides, in the FRAP test, the significantly ($P < 0.05$) superior activity was attributed to the extract from MAE with the IC_{50} value of 3.95 ± 0.03 mg/mL compared to the one from CE with IC_{50} of 4.54 ± 0.15 mg/mL.

About the activity in the β-carotene assay, it was found that the IC50 (3.43 ± 0.15 mg/mL) of the extract from MAE was also significantly lower ($P < 0.05$) than the IC50 of the extract from CE (7.16 ± 0.17 mg/mL).

Ghasemi, Ghasemi, and Ebrahimzadeh (2009) assessed the DPPH• radical scavenging capacity of thirteen citrus peels, including *C. × paradisi* from Iran. They found that the IC_{50} of their methanolic extracts procured by the percolation method varied from 0.6 to 3.8 mg/mL.

The DPPH assay results were also lower than those provided from MAE of Citrus lemon peels extract (Dahmoune et al., 2013).

According to Nayak et al. (2015), the *C. Sinensis* peels extract that resulted from MAE, exhibited higher DPPH radical scavenging capacity (IC_{50} = 337.16 ± 8.45 mL/L) than the extracts obtained by Ultrasound and Accelerated-Assisted Solvent Extraction (UAE) (IC_{50}: 437.45 ± 1.30 mL/L), conventional solvent (CSE) (IC_{50}: 357.36 ± 6.02 mL/L) and accelerated-solvent (ASE) (IC_{50}: 450.44 ± 4.48 mL/L) methods. The same trend was recorded by Hayat et al. (2009) where the extract of citrus mandarin peels achieved with MAE had higher antioxidant activity than those of ultrasonic extraction (USE) and rotary extraction (RE) techniques.

Menichini et al. (2016) reported that the IC_{50} of *Citrus medica* L. peel extract acquired by maceration in terms of DPPH, $ABTS^{\bullet+}$, and β-Carotene bleaching tests were 0.81, 3.48 and 0.23 mg/mL, respectively. Otherwise, Castillo, Dávila-Aviña, Heredia, and Garcia (2017) studied the antioxidant activity of three Citrus by-product extracts by DPPH and ABTS methods. They noticed that the best DPPH radical scavenging activity was assigned to the *C. aurantium* by-product extract (90.1 ± 0.6%). For the ABTS assay, the TEAC values varied from 14.8 ± 0.5 to 19.8 ± 0.1 μmol Trolox Equivalent/g. Rodsamran and Sothornvit (2019) reported the values of antioxidant activity of lime (*Citrus aurantiifolia*)

Table 5
Antioxidant activity of *Citrus× paradisi* peels using MAE (Microwave Assisted Extraction) and CE (Conventional Extraction) methods.

Extraction methods	TPC (mg GAE/g dw)	IC_{50} (mg/g dry extract)			
		Reducing power	ABTS	DPPH	β-carotene/ linoleic acid
MAE	31.10 ± 2.11[b]	3.95 ± 0.03[a]	1.90 ± 0.02[a]	12.81 ± 0.14[a]	3.43 ± 0.15[a]
CE	26.75 ± 1.15[a]	4.54 ± 0.15[b]	2.02 ± 0.01[b]	20.89 ± 0.41[b]	7.16 ± 0.17[b]

MAE: Microwave assisted extraction, CE: Conventional extraction. Results are expressed as means ± standard deviation. n = 3, a, b: *indicates significantly different samples ($P < 0.05$).*

peel waste extracted by MAE of 19 and 465 μM Trolox/g using DPPH and ABTS assays, respectively.

The *Citrus medica* peel water extract achieved using MAE exhibited a potent capacity to scavenge DPPH$^{\bullet}$ radical (IC_{50} = 0.022 mg/mL) (Mahdi et al., 2019). By comparing our results with previous work, unfortunately, the data are different; this could be due to uncontrolled external factors: agro-climatic conditions, soil composition, harvesting periods, and to controlled factors: extraction methods and conditions (Ghasemi et al., 2009).

The citrus peel contains considerable amounts of highly active antioxidants (De Moraes Barros, De Castro Ferreira, & Genovese, 2012). According to the literature, the citrus peel antioxidant power is due to its richness in flavonoids, phenolic acids, and vitamin C (Kurowska & Manthey, 2004). The identified phenolics in these by-products are hesperidin, narirutin, nobiletin, and tangeritin, which are scavengers of free radicals (Chen, Tait, & Kitts, 2017).

The lower activity of the extract obtained by CE could result from prolonged extraction time, which resulted in the exposure to adverse conditions such as light and oxygen (Hayat et al., 2009). On the other hand, the higher activity of the extract from MAE could be explained by microwave treatment, which affects the structure of the cell due to the sudden increase in the temperature and internal pressure, which can release antioxidant substances (Dahmoune et al., 2013).

3.5. Antioxidant power of the new packaging

The antioxidant capacity of films containing the two extracts applied into the packaging at different concentrations was measured, following the procedure developed by (Pezo et al., 2006; Pezo, Salafranca, & Nerín, 2008), where the antioxidant performance is measured as free radical scavenging activity. The results obtained for the packaging exposed to an enriched atmosphere of free radicals are shown in Fig. 3. The results are expressed as % of hydroxylation, as the non-scavenged free radicals crossing the plastic bag arrive at the salicylic solution and produce the hydroxylated compound 2,5-dihydroxybenzoic acid (2, 5-DHB). In the absence of radical scavenging activity, 100% hydroxylation is achieved. There was a significant difference ($P < 0.05$) between the different concentrations tested. The maximum antioxidant capacity was noted with the film prepared with 10% of the MAE extract (35.28 ± 2.36% of hydroxylation). A significant diminution ($P < 0.05$) of hydroxylation compared to the blank (100%) was obtained (Fig. 3).

The data acquired confirmed that the free radicals cross the LDPE film and interact with the antioxidant extract (scavenger) between LDPE and PET sheets. This performance was already demonstrated in previous work (Vera et al., 2016). Direct contact between the scavenger and the food or antioxidants releases into it is not needed. The results of antioxidant efficiency are consistent with those of films prepared with extract of green tea reported by previous studies (Colon & Nerin, 2012), and those of active ingredients based on oregano and cinnamon and more antioxidants than those active films prepared with lemongrass, ginger, propolis, rosemary, sage and bay leaves extracted with 60% of ethanol (Oudjedi et al., 2019) and coffee extract (Colon & Nerin, 2012).

The responsible for antioxidant power can be ascribed to the phenolics of the MAE extracts characterized using UPLC-MS^E (Table 4). The comparable finding was previously established since the grapefruit (*Citrus grandis*) peel includes flavonoids known for their strong antioxidant power (Sârbu et al., 2012). The results reported by several authors (Liu et al., 2015; Wang, Dong, Men, Tong, & Zhou, 2013) showed that the antioxidant activity of PPF films (grapefruit peel flour) significantly increased ($p < 0.05$) with the increase in the concentration of TP (tea polyphenol).

4. Conclusions

In this investigation, the adopted MAE procedure allowed a higher recovery yield of total phenolic compounds from *Citrus* × *paradisi* peels than CE. This green technique provided a higher concentration of antioxidant compounds in a limited period and used only small solvents. The extracts resulting from MAE and CE were incorporated into a multilayer LDPE/PET, where they were successful in scavenging free radicals, thus acting as strong antioxidants. Comparing the same concentrations (5%) of both extracts, the MAE extract gave the best results. Thus, the *C.* × *paradisi* by-products can be valorized by incorporating them into the food packaging films to improve their antioxidant power.

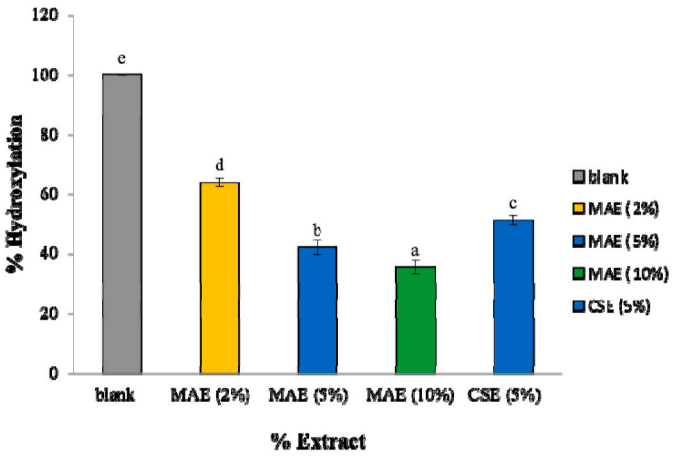

Fig. 3. Antioxidant capacity of active film samples subjected to hydroxylation after 24 h. The blank (plastic film without natural extract) is regarded as the 100% reference, MAE (Microwave-Assisted Extraction) (2, 5 and 10%): the film contained the *Citrus* × *paradisi* peel extract at different percentages obtained by MAE method, CE (conventional extraction) (5%): the film contained the *Citrus* ×*paradisi* peel extract at percentages of 5 obtained by CE method n = 3, a–e: Different letters indicates significantly different samples ($P < 0.05$).

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Conflict of interest

We wish to confirm that there are no conflicts of interest associated with this publication, and there has been no significant financial support for this work that could have influenced its outcome.

CRediT authorship contribution statement

Ghania Kaanin-Boudraa: Methodology, Validation, Investigation, Data curation, Writing – original draft. **Fatiha Brahmi:** Methodology, Validation, Investigation, Data curation. **Magdalena Wrona:** Conceptualization, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Supervision. **Cristina Nerín:** Conceptualization, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Messaad Moudache:** Conceptualization, Methodology, Validation, Investigation, Data curation. **Khokha Mouhoubi:** Conceptualization, Methodology, Validation, Investigation, Data curation. **Khodir Madani:** Conceptualization, Resources, Supervision, Project administration, Funding acquisition. **Lila Boulekbache-Makhlouf:** Conceptualization, Resources, Supervision, Project administration, Funding acquisition.

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