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Original research

Extraction of phenolic compounds from *Agrimonia eupatoria* using microwave and ultrasound-assisted extraction methods

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A B S T R A C T

Agrimonia eupatoria (AE) is commonly used as a medicinal plant in Iran. In this study, microwave and ultrasound-assisted extraction (MAE and UAE) methods have been developed to extract phenolic compounds from AE. In addition, the impact of operational variables such as the solvent composition (ethanol and water), microwave and ultrasonic power, and extraction time on the content of total phenolic compounds (TPC) and antioxidant activity (AA) was evaluated through response surface methodology (RSM). The optimized conditions of MAE were as follows: microwave power was 200 W, extraction time was 15 min and ratio of ethanol to water was 0.78 v/v. Under these conditions, the maximum content of TPC and AA were 326.11 mg GAE/100g and 52.25% respectively. The maximum amount of TPC in UAE method was 355.12 mg GAE/100g. Antioxidant activity of about 75.92% was also achieved. The optimum extraction ultrasonic power, time and ratio of ethanol to water were defined as 100 W, 41.82 min and 1.17 v/v, respectively. High-performance liquid chromatography (HPLC) revealed the presence of five different types of phenolic compounds, namely chlorogenic acid, quercetin, rutin, cumaric acid and apigenin in the MAE and UAE extracts. The results indicated UAE was more efficient than the MAE to extract phenolic compounds from AE.

Keywords: *Agrimonia eupatoria* extract; Microwave; Ultrasound; Antioxidant activity

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1. Introduction

Agrimonia eupatoria (AE), Rosaceae, commonly known as agrimony, is an erect, perennial herb, up to 100 cm high, mostly unbranched, with a cylindrical stem (Barnes et al., 1996). Stems and leaves of AE contains volatile oils, flavonoids, apigenin, luteolin, quercetin, kaempferol, tiliroside, triterpene glycosides including euscapic acid and tormentic acid, phenolic acids and 3-20% tannins (Watkins et al., 2012). AE is used in traditional medicine to treat inflammatory and oxidative related diseases. The aerial parts of agrimony are applied in various forms including: infusions, decoctions, or tinctures in traditional medicine, due to their antioxidant, anti-inflammatory, astringent, and diuretic properties (Santos et al., 2017). This plant grows in north and northwest of Iran and is commonly used as a medicinal plant.

Phenolic compounds (tocopherols, flavonoids, and phenolic acids) are responsible for the fruits' red colour, juice, wines, substrates for enzymatic browning, and they involved in flavour properties (Cheynier et al., 2012). The beneficial effects derived from phenolic compounds have been attributed to their antioxidant activity. These compounds could be a major determinant of antioxidant potentials and a natural source of antioxidants of foods (Sharifi & Khoshnoudi-Nia, 2022).

The isolation of plants bioactive compounds is considered as the first step of extraction. Extraction of phenolic compounds from medicinal plants can be carried out in various ways. The most suitable methods should be applied in the extraction so as to obtain useful compounds with low levels of impurity and damage (Sharifi et al., 2019). There is an increasing demand for new extraction techniques to decrease extraction times and consumption of chemicals solvents; in addition, to boast yields and quality of the

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extract and to prevent environmental pollution (Rajaei et al., 2010). Novel extraction methods including Ultrasound-Assisted Extraction (UAE) (Maran et al., 2017), Microwave-Assisted and Ultrasound-Assisted Extraction (Da Rocha & Noreña, 2020), Microwave-Assisted Extraction (MAE) (Ballard et al., 2010), Pressurized liquid extraction (Katsinas et al., 2021), Ultrasound-Assisted and ohmic extraction (Shahidi et al., 2020), Supercritical Fluid Extraction (SFE) (Vatai et al., 2009), high-pressure carbon dioxide (HPCD) technique (Sharifi et al., 2019), ohmic heating (Brochier et al., 2016), pulsed electric field (El Darra et al., 2013), and accelerated solvents (Hossain et al., 2011) are fast and efficient for extracting bioactive compounds from plant matrixes. In recent years, UAE and MAE techniques have become very popular for polyphenols extraction.

This study aimed to develop MAE and UAE methods to extract phenolic compounds from *Agrimonia eupatoria* in order to develop the use of natural polyphenols in the food industry instead of synthetic antioxidants.

2. Material and Methods

2.1. Materials

Stems and leaves of *Agrimonia eupatoria* (AE) were collected in July 2017, in Qazvin province, Iran. Stems and leaves were separated then leaves were dried under a fan at room temperature. Dried AE leaves was milled (model 320P, Pars-Khazar, Tehran, Iran) to a fine powder, passed through a mesh number 60 sieve and was sealed in a brown bottle and kept at 4-5°C until the extraction process. All chemicals in analytical grade were purchased from Merck Company (Darmstadt, Germany).

2.2. Microwave-assisted extraction (MAE)

The extraction of AE leaves phenolic compounds through a microwave oven (Panasonic, NN-CD997S) was carried out under different extraction conditions according to the experimental design shown in Table 1. 3 g of AE leaves powder were mixed with solvent (ratio of solvent to plant was 80:20). After the extraction time was finished, the samples were centrifuged (model: HERMLE Z 323 K, Technik GmbH Hermle Labor, Germany) at 4000 rpm for 15 minutes and filtered through a 0.45 µm filter paper and then kept in the dark glass bottles (Rajaei et al., 2010).

Table 1. Coded levels of independent variables (different extraction conditions) used in the RSM design.

Independent variables	Coded levels		
	-1	0	+1
MAE time (A; min)	15	10	5
Microwave power (B; W)	400	300	200
MAE ratio of ethanol to water (C; v/v)	1.5	1	0.5
UAE Time (A; min)	60	40	20
Ultrasonic power (B; W)	200	150	100
UAE ratio of ethanol to water (C; v/v)	1.5	1	0.5

2.3. Ultrasound-assisted extraction (UAE)

UAE was performed in an ultrasonic bath (DT 255 H, Bandelin Co. Germany; nominal output power of the ultrasound generator: 0-300 W, 50 kHz Numerical Control Ultrasonic Cleaner). The dried AE leaves powder (3g) mixed with solvent (ratio of solvent to plant was 80:20), and AE phenolic compounds were extracted under various conditions based on the experimental design shown in Table 1. The extract was centrifuged at 4000 rpm for 15 minutes and filtered through a 0.45 µm filter paper and then kept in the dark glass bottles (Rajaei et al., 2010).

2.4. Determination of antioxidant activity (AA)

The antioxidant activity of the extract was determined using DPPH (2, 2-diphenyl-1-picrylhydrazyl) method as described by Galvez et al. (2007) with minor modifications. The extract (0.5 mL) with 3.5 mL of 0.06 mM DPPH was diluted with ethanol. The mixture was incubated at room temperature in the dark place for 20 min. The percentage inhibition of DPPH was determined by measuring the absorbance at 517 nm using a spectrophotometer (UV-9200; Beijing Rayleigh Analytical Instrument Co., Beijing, China). The control sample was prepared without adding extract. The antioxidant activity was measured using Eq. (1):

$$\text{DPPH}\ (\%) = \frac{A_{\text{blank}} - A_{\text{sample}}}{A_{\text{blank}}} \times 100 \qquad (1)$$

where A_{blank} and A_{sample} control and extract absorbance at 517 nm, respectively.

2.5. Determination of total phenolic contents (TPC)

TPC were measured by Folin–Ciocalteu method. 0.5 ml of the extracts was mixed with distilled water (1.8 ml), a Folin–Ciocalteau reagent (0.1 ml) and 2 ml of sodium carbonate (7.5% w/v). The tubes were vortexed for 15 S and allowed to stand for 30 min at room temperature for color development. Absorbance was read at 765 nm using UV-Vis spectrophotometer (SINCO, Seoul, South Korea). The results were expressed in terms of mg Gallic Acid Equivalents per gram of sample (mg GAE/100g) (Vatai et al., 2009).

2.6. HPLC identification of TPC

HPLC analyses were performed using a HPLC system (YOUNGLIN, Korea) equipped with a pump (SP930D), detector (UV730D), C (18) column (250 mm × 4.6 mm, 5 microm) and an autosampler, for samples including the highest level of TPC and extracted with the optimized UAE and MAE methods. The extract filtered through a 0.45 µm Whatman polypropylene filter before injection. The Mobile phase consisted of acetonitrile in water (solvent A) and 0.1% (v/v) phosphoric acid (solvent B) with flow rate of 1 ml/min. The injection volume was 20 µL and the temperature was fixed at 30°C. The following elution program was conducted during 0–50 min with a flow rate of 1.5 mL min^{-1} from phase B, 51–65 min with a flow rate of 1.5 mL min^{-1} from phase B and during 66– 85 min with a flow rate of 1 mL min^{-1} of 100% from phase A (Thabti et al., 2012).

2.7. Experimental design and statistical analysis

Optimization of extraction conditions of phenolic compounds from AE leaves was carried out using response surface methodology (RSM). A Central Composite Design consisting of twenty experimental runs was employed including six replicates at the center point. All the runs were conducted in duplicate. The design variables were MAE and UAE time (X_1, min), MAE and UAE power (X_2, W), MAE and UAE ratio of ethanol to water (X_3, v/v), while the dependent variables were TPC and AA. The coded and uncoded independent variables which were used in the RSM design have been listed in Table 1. Analysis of data and calculation of predicted responses were carried out through using the Minitab software (version 17). A second-order polynomial equation was used to express the responses as a function of the independent variables (Eq. 2):

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{11}A_2 + b_{22}B_2 + b_{33}C_2 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 \quad (2)$$

where Y represents the measured response variables including TPC and AA, b_n stands for regression coefficients which represent the linear, quadratic and interactive effects of the variables. The experimental and predicted values were compared to determine the validity of the model.

Optimal conditions for the extraction AE leaves phenolic compounds were conducted through the application of numerical optimization of RSM. Extraction conditions were considered as optimum if TPC and AA reached their maximum levels.

3. Results and Discussion

3.1. Statistical analysis

According to the statistical analysis and the p-value from the F-test ($p \leq 0.05$), the non-significant lack of fit value ($p \geq 0.05$), the values of R-Squared and the adjusted R-Squared, and the value of the coefficient of variation, the selected model was suitable. The ANOVA results reveal that all the variables of the fitted model were statistically significant ($p \leq 0.05$) and thus the proposed model was quite sufficient in comparison with predicting responses. All the factors with non-significant F-test values were removed from the model after the variables influence was evaluated (Lee et al., 2006; Sharifi et al., 2019). Furthermore, the interactive influence of MAE and UAE time, MAE and UAE power, MAE and UAE ratio of ethanol to water, on the TPC and AA was discussed.

3.2. Effects of microwave-assisted extraction (MAE) conditions on TPC and AA

The results revealed the highest amount of phenolic compounds was due to extraction time of 15 min, microwave power of 400 W and ratio of ethanol to water of 0.5 v/v. As it was shown in Fig. 1 (D, E and F) with an increase in the microwave power and extraction time, TPC was increased. Moreover, increasing the ethanol to water ratio initially increased and then the total phenol content was decreased. Applying ethanol solvent in a mixture with water is able to extract more phenolic compounds from plant tissues than the pure state. Adding water to organic solvents creates a relatively polar environment and therefore phenolic compounds were extracted in more amount and variety (Chirinos et al., 2007).

Svarc-Gajic et al. (2013) observed that the mixture water–methanol in the proportion 30:70 showed to be the most efficient solvent for extracting total phenolic from rosemary. Results obtained from other studies about the determination of natural phenols in other samples (Lapornik et al., 2005; Svarc-Gajic et al., 2013) proved results of this study.

The direct relation between extraction time and TPC is due to making the opportunity to extract phenolic compounds through increasing time. The researchers proved that high temperatures and long time can damage phenolic compounds and thus reduce those (Suzuki et al., 2002). The total phenol content was increased through rising microwave power making the plant cell wall destructed; therefore, phenolic compounds increased (Suzuki et al., 2002).

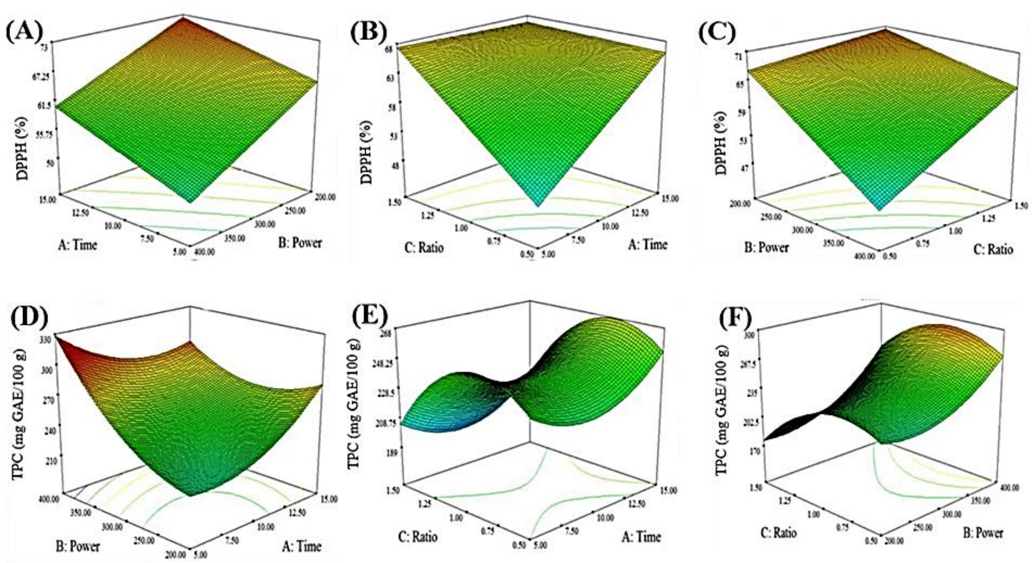

Fig. 1. Response surface for the effects of MAE time (A and D), ratio of ethanol to water (B and E) and power (C and F) on the total phenolic compounds (TPC) and antioxidant activity (AA).

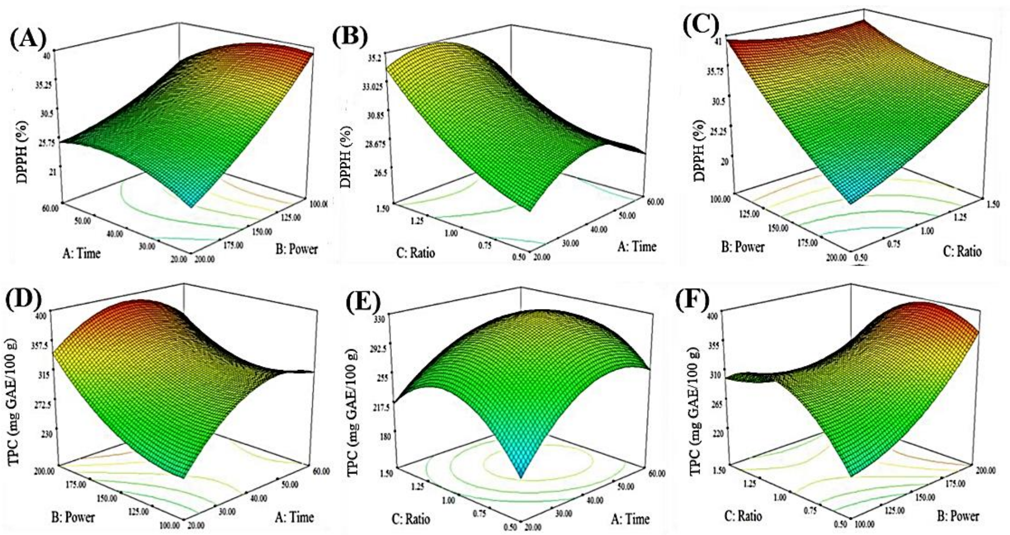

Fig. 2. Response surface for the effects of UAE time (A and D), ratio of ethanol to water (B and E) and power (C and F) on the total phenolic compounds (TPC) and antioxidant activity (AA).

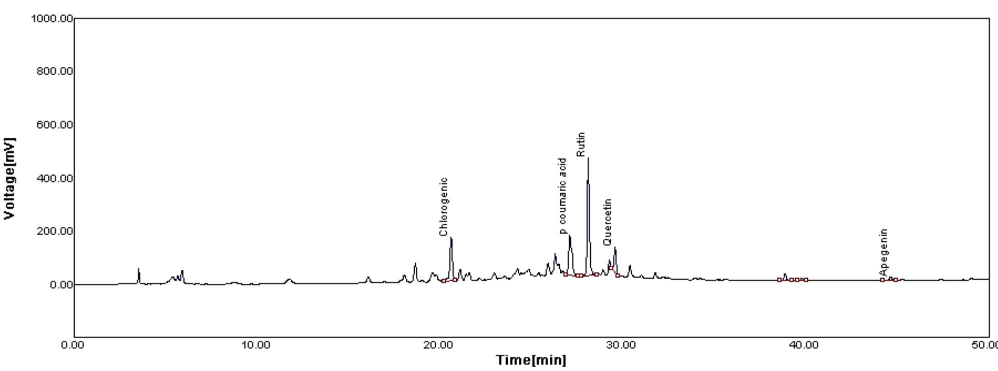

Fig. 3. HPLC chromatogram of major phenolic compounds of *Agrimonia eupatoria* extract (MAE).

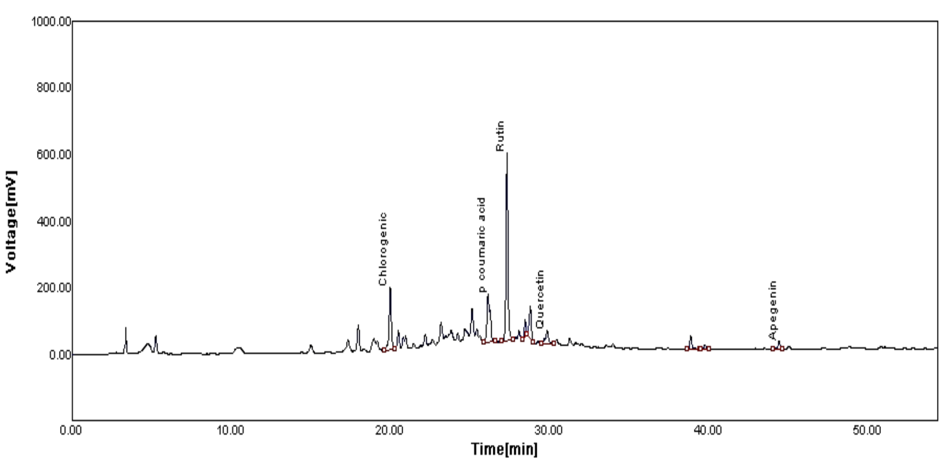

Fig. 4. HPLC chromatogram of major phenolic compounds of *Agrimonia eupatoria* extract (UAE).

Microwave power, extraction time and ethanol to water ratio had significant effect on the amount of extracted phenolic compounds. This finding was in agreement with previous studies (Svarc-Gajic et al., 2013; Ballard et al., 2010; Sutivisedsak et al., 2010; Proestos et al., 2008; Pan et al., 2003).

The linear effects (X), the quadratic factors (X^2) and also the interactive effects of time, power and ratio of ethanol to water on the TPC were significant. Considering the factors with a statistically significant effect, the equation for the fitted response has been provided below:

$$\text{Total phenol}_{\text{MAE}}\ (\text{mg GAE}/100\ \text{g}) = 212.96 + 0.08X_1 - 0.67X_2 + 182.7X_3 + 0.82X_1^2 + 0.002X_2^2 - 122.75X_3^2 - 0.04X_1X_2 - 0.59X_1X_3 + 0.11X_2X_3 \quad (3)$$

The R-Squared (R^2), Adj R-Squared of the predicted model and the p value for the lack-of-fit test were 0.9974, 0.9950 and 0.923, respectively. These values can indicate that the proposed model can accurately predict the response.

It can be seen that the extracted solution of AE under MAE conditions has had a high capability in scavenging the DPPH free radicals. The highest amount of AA was related to extraction time of 15 min, microwave power of 200 W and ratio of ethanol to water of 1.5 v/v (Fig. 1, A, B and C).

Based on Fig. 1 (A, B and C) the three factors of time, power and ethanol to water ratio had different impacts on antioxidant activity. The antioxidant activity decreased by increasing microwave power and extraction time, ethanol to water ratio was also directly related to this response.

The results of Xu et al. (2018) indicated that the MAE processing for bioactive compounds extraction of *E. ulmoides* leaf, can greatly accelerate the release of natural antioxidants. The MAE exhibited significant advantages in terms of high extraction efficiency of bioactive components from the plant materials (Xu et al., 2018).

Li et al. (2017) established the MAE method to extract antioxidants from the fruit of *Gordonia axillaris*. Their results showed that the antioxidant capacity of the extract obtained by MAE method was stronger than that obtained by other methods.

The linear effects (X), the interactive effect of time, power, and ratio of ethanol to water on the AA were significant. The regression coefficient indicated that the linear effects had more positive impact on this response. However, the quadratic factors of time, power and ratio of ethanol to water have had no statistically significant effect on the AA. The factors were therefore removed from the model. The fitted equation for this response has been provided in the following section:

$$\text{DPPH}_{\text{MAE}}\ (\%) = 84.64 + 2.52X_1 - 0.32X_2 + 28.96X_3 + 0.001X_1X_2 - 1.84X_1X_3 + 0.06X_2X_3 \quad (4)$$

Considering the p value for the lack-of-fit test (0.757), R-Squared (0.9740) and Adj R-Squared (0.9507) the proposed response prediction model is reasonably accurate.

3.3. *Effects of ultrasound-assisted extraction conditions on TPC and AA*

Fig. 2 (D, E and F) presents the effects of the independent variables on TPC. The results showed the highest amount of phenolic compounds in UAE was obtained at time of 48 min, power of 200 W and ethanol to water ratio of 1 (401.48 mg GAE/100g). The concentration of phenolic compounds has increased by an increase in the ultrasonic power, extraction time and ethanol to water ratio to 1. In line with these findings, Yingngam et al. (2014) found that an increase in the ultrasonic power and extraction time resulted in the phenolic compound concentration increase. Based on their results, the phenolic compounds of *Cratoxylum formosum* ssp. *formosum* leaves increased significantly from 38.40 mg GAE/g to 41.37 mg GAE/g during extraction time of 10 min and 20 min, respectively. The polyphenols are sensitive to high temperatures. High amounts of TPC in the extract obtained by UAE are resulted from the extraction process at lower temperature (De Guiné & Barroca, 2014). In UAE, the physicochemical properties of the plant matrix might be affected by ultrasound waves; therefore these properties might be altered (Shahidi et al., 2020; Dhanani et al., 2017).

Statistical analysis results indicated that the linear effects (X), the quadratic factors (X^2) and also the interactive effect of time, ultrasonic power and ratio of ethanol to water have had statistically significant effects on the TPC. Considering the factors with a significant effect, Eq. (5) for the fitted response has been provided below:

$$Total\ phenol_{UAE}\ (\text{mg GAE}/100\ g) = -361.72 + 14.20X_1 - 0.60X_2 + 731.06X_3 - 0.11X_1^2 + 0.011X_2^2 - 225.87X_3^2 - 0.017X_1X_2 - 1.45X_1X_3 - 1.44X_2X_3 \quad (5)$$

The value of the R-Squared (R^2) and Adj R-Squared for the predicted model and the p value for the lack-of-fit test were indicated to be 0.9256, 0.8585, and 0.324 respectively. These values can represent that the proposed model can accurately predict the response.

Considering statistical analysis results and Fig. 2 (A, B and C), it can be seen that the extracted solution of AE under UAE conditions had a high capability to scavenge the DPPH free radicals. The percentage of DPPH radical scavenging activity ranged between 15.75 and 40.51%. In other words, the highest radical scavenging activity was achieved in 20 min, 100 W and ethanol to water ratio of 1.5 v/v.

Three factors of time, ultrasonic power and ethanol to water ratio had different effects on antioxidant activity, so that ultrasonic power increase let to this parameter decrease. Ethanol to water ratio had a direct relation with antioxidant activity. An increase in antioxidant activity was observed through increasing the extraction time to 20 min, and then this response decreased. As mentioned previously, increasing the time more than 20 min at high ultrasonic power can lead to a decrease in the amount of antioxidant activity which is due to the destruction of phenolic compounds under hard extraction conditions (Martino et al., 2006).

Increasing the concentration of phenolic compounds directly increases different extracts ability to scavenge the DPPH free radicals. DPPH radicals are reduced by phenolics' hydrogen donating ability (Prasad et al., 2005).

Tsai et al. (2014) were determined the antioxidant activities of *P. emblica* ethanol extracts obtained by UAE in terms of evaluation total antioxidant activity, metal chelating activity, and reducing power; *P. emblica* extracts showed high antioxidant activity.

Previous study also revealed that high antioxidant activity was detected in yellow tea extracts obtained by UAE (Horzic et al., 2012). These findings suggest that UAE is an efficient extraction method for high antioxidant compounds from different natural sources.

The linear effects (X), the quadratic factors (X^2) and the interactive effect of time, ultrasonic power and ratio of ethanol to water on the AA were significant. The fitted equation for this response has been provided in the following section.

$$\begin{aligned} \mathrm{DPPH_{UAE}}\ (\%) = {} & 83.37 + 0.19X_1 - 0.51X_2 - 20.76X_3 \\ & - 0.005X_1^2 + 0.0005X_2^2 + 4.81X_3^2 \\ & + 0.002X_1X_2 - 0.094X_1X_3 \\ & + 0.13X_2X_3 \end{aligned} \quad (6)$$

R-squared (R^2) and Adj R-Squared of the predicted model and the p value for the lack-of-fit test were 0.9942, 0.9898 and 0.747 respectively.

3.4. Optimization of microwave and ultrasound-assisted extraction (MAE and UAE) condition

Determination of optimum operating MAE and UAE condition was carried out by using numerical optimization of RSM. The optimized conditions of MAE were as follows: microwave power was 200 W, extraction time was 15 min and ratio of ethanol to water was 0.78 v/v. Under these conditions, the maximum content of TPC and AA were 326.11 mg GAE/100g and 52.25% respectively. In order to verify the predictive capacity of the model, confirmation test was done. TPC and AA in the optimum condition predicted evaluated with three replications. AA in these conditions was 51.11 ± 0.80% and TPC was 325.18 ± 0.60 mg GAE/100g.

The maximum amount of TPC and AA in UAE method was 355.12 mg GAE/100g and 75.92%, respectively. The optimum extraction ultrasonic power, time and ratio of ethanol to water were defined as 100 W, 41.82 min and 1.17 v/v, respectively. Results of confirmation test for UAE showed 75.29 ± 0.24% and 355.01 ± 0.10 mg GAE/100g for TPC and AA respectively.

These results confirm the predictability of the model to extract phenolic compounds from AE under the employed experimental conditions.

3.5. Chromatographic identification of the major phenolic compounds in the AE leaves extract

According to Fig. 3, five types of phenolic compounds were found in the optimized extracted sample with MAE method in different quantities namely chlorogenic acid (4.91 mg/g), quercetin (0.87 mg/g), rutin (78.96 mg/g), cumaric acid (1.90 mg/g), and apigenin (0.14 mg/g).

Chlorogenic acid, quercetin, rutin, cumaric acid and apigenin of optimezed extracted sample with UAE method were 5.49 mg/g, 0.63 mg/g, 103.85 mg/g, 2.14 mg/g and 0.23 mg/g, respectively (Fig. 4). Furthermore, the highest amount of measured phenolics was related to rutin in both methods.

Santos et al. (2017) were recorded flavan-3-ols, quercetin, kaempferol, apigenin, luteolin derivatives, and in lesser extent, agrimoniin, p-coumaric acid, and ellagic acid in *Agrimonia eupatoria* L. by HPLC-PDA-ESI/MS.

3.6. Comparison between extraction methods

The results of the one-way Analysis of Variance (Duncan test) indicated UAE was more statistically efficient than the MAE to extraction phenolic compounds from AE. TPC and AA of MAE at the optimal point were 326.11 mg GAE/100g and 52.25 % respectively while TPC and AA in UAE method at the optimal point were 355.12 mg GAE/100g and 75.92%, respectively. These results are a verification of the results obtained by Rodrigues et al. (2008) and Balasundram et al. (2006). Rajaei et al. (2010) demonstrated that in the extraction of Pistachio Green Hull, UAE was more effective than other methods.

The ultrasound-assisted extraction gave higher total phenolic content and antioxidant activity during the shorter extraction time; therefor this technique is considered better to extract phenolic compounds (Gajic et al., 2019). This finding was in agreement with several previous studies which concluded that UAE has a good potential for bioactive compounds extraction (Rodrigues et al., 2008; Maran et al., 2017; Gajic et al., 2019).

4. Conclusion

The optimized conditions of MAE were as follows: microwave power was 200 W, extraction time was 15 min and ratio of ethanol to water was 0.78 v/v. Under these conditions, the maximum content of TPC and AA were 326.11 mg GAE/100g and 52.25% respectively. The maximum amount of TPC in UAE method was 355.12 mg GAE/100g. Antioxidant activity of about 75.92% was also achieved. The optimum extraction ultrasonic power, time and ratio of ethanol to water were defined as 100 W, 41.82 min and 1.17 v/v, respectively. The results indicated UAE was more efficient than the MAE to extraction phenolic compounds from AE. UAE is a green process for the preparation of extracts rich in natural antioxidants aimed at using in food industry to replace synthetic antioxidants. High-performance liquid chromatography (HPLC) revealed the presence of five different types of phenolic compounds, namely chlorogenic acid, quercetin, rutin, cumaric acid and apigenin in the MAE and UAE extracts.

Acknowledgment

Not applicable.

Conflict of interest

Authors declare that they have no conflict of interest.

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