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Ultrasound assisted extraction of phenolic compounds from *P. lentiscus* L. leaves: Comparative study of artificial neural network (ANN) versus degree of experiment for prediction ability of phenolic compounds recovery

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ABSTRACT

Design of experiments (DOE) based on central composite design (CCD) and artificial neural networks (ANNs) were efficaciously applied for the study of the operating parameters of ultrasound assisted extraction (UAE) in the recovery of phenolic compounds from *P. lentiscus* leaves. These models were used to evaluate the effects of process variables and their interaction toward the attainment of their optimum conditions. Under the optimal conditions (13.79 min extraction time, 33.82 % amplitude and 30.99 % ethanol proportion), DOE and ANN models predicted a maximum response of 140.55 and 138.3452 mgGAE/gdw, respectively. A mean value of 142.76 ± 19.98 mgGAE/gdw, obtained from real experiments, demonstrated the validation of the extraction models. A comparison between the model results and experimental data gave high correlation coefficients (R^2_{ANN} = 0.999, R^2_{RSM} = 0.981), adjusted coefficients (R_{adjANN} = 0.999, R_{adjRSM} = 0.967) and low root mean square errors (RMSE$_{ANN}$ = 0.37 and RMSE$_{RSM}$ = 4.65) and showed that the two models were able to predict a total phenolic compounds (TPC) by green extraction ultrasound process. The results of ANN were found to be more consistent than DOE since better statistical parameters were obtained.

1. Introduction

Nowadays, consumers are highly aware of the close relationship between nutrition and health and they want to include health-promoting ingredients in their diets. Therefore, natural ingredients recovered from vascular plants have specific dietary and functional properties and can be utilized effectively to develop food additives or supplements with high nutritional value (Gruenwald, 2009). For example, the Food and Drug Administration (FDA) classifies ferulic acid as an antioxidant in the list of food additives (Lupien, 2002). Whole foods have been estimated to have between 5,000 and 25,000 individual phytochemicals (Thabit et al., 2015). Among these, phenolic compounds are secondary metabolites, ubiquitous widely exist in nature and food-industry by-products. They are differentiated from one another by their structure and molecular weight, and the resulting physicochemical and biological properties. Due to this enormous variety, there are reports of more than 10000 phenolic molecules and the list continues expanding (Vázquez et al., 2015). They show a large diversity of structures including simple phenols (C6); phenolic acids and related compounds (C6–C1); acetophenones and phenyl acetic acids (C6–C2); cinnamic acids, cinamyl aldehydes, and alco-

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hols (C6–C3); coumarins, isocoumarins, and chromones (C6–C3); flavonoids (C15); biflavonyls (C30); stilbenes (C6–C2–C6); benzophenones and xanthones (C6–C2–C6); quinones (C6, C10, C14); betacyanins (C18); and lignans, lignins, tannins, and phlobaphenes (which are dimmers, oligomers, or polymers).

All these phenolics are well documented and established, while they exhibit great attention due to their ability to promote benefits for human health such as the reduction in the incidence of some degenerative diseases like cancer, diabetes, reduction in risk factors of cardiovascular diseases, anti-inflammatory, antioxidant, antimutagenic, antimicrobial, anticarcinogenic activities and help in the prevention of cytotoxic effects of oxidized low-density lipoprotein (LDL) and consequently atherosclerosis (Delpino-Rius et al., 2015). Due to these omnipresence and countless beneficial characteristics for human health as well as the recent consumer demand for "all natural", researches have been intensified aiming to valorization of plants, agricultural by-products and agro-industrial residues as natural-identical ingredient antioxidant additives and colorants instead of synthetic counterparts which proved negative health effects, such as butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) (Dawidowicz et al., 2015). *Pistacia lentiscus* products have a wide range of uses in food industry due to activities related to their secondary metabolites, such as flavonoids, polyphenols and phenolic acids (Bampouli et al., 2014).

This diverse range of biological properties makes spice phenolics an interesting target for their extraction conditions. Currently, extraction is being carried out using traditional processing technologies including solvent extraction (both liquid–liquid and solid–liquid extraction) by assistance of different processes like mechanical agitation, pressing, or heating systems. These processes are still popular and the most regarded amongst all the conventional extraction methods because they have been well established and are easy to perform and to operate. However, these methods have been associated with economic impact, high solvent consumption, longer extraction times (up to 1500 min or more) and an increased risk of thermal degradation of sensitive components (Spigno et al., 2007).

These shortcomings have led to the consideration of the use of new "eco-friendly" techniques in separation, which typically use less solvent and energy (Chemat et al., 2012). In last decade, few alternative technologies as energy saving including ultrasound assisted extraction (UAE) (Dahmoune et al., 2014), supercritical fluid extraction (SFE) (Veggi et al., 2014), pressurized liquid extractions (PLE) (Machado et al., 2015) and microwave assisted extraction (MAE) (Dahmoune et al., 2015) are used.

From the literature review, the use of ultrasound is increasingly employed as an alternative method over the traditional in extraction of natural products because they are shortening of processing and residence times (they can now be completed in minutes instead of hours with high reproducibility) and accelerated heat and mass transfer, eco-friendly, with strongly decreased solvent consumption and quality of the extracts (Ramić et al., 2015). In all cases, for keeping these advantages, production of natural functional ingredients from natural sources, represents: a unique low-cost resource. The increasing number of investigations published in this area highlights unyielding interests in the application of mathematical models for the antioxidants-making optimization-process.

Degree Of Experiment (DOE) based on Response Surface Methodology (RSM) is the commonly used optimisation tool that optimises the process variables during the extraction of natural phenolic compounds from the plant sources (Gong et al., 2012). RSM is one of the DOE relevant multivariate techniques that can deal with experimental design, statistical modeling and process optimization (Hafizi et al., 2013b). RSM generally applies the central composite design and Box–Behenken design (Dahmoune et al., 2013). It have been widely used in the industries to develop their production as well as to optimise processes that have several factors that influence the responses of the final product. RSM is a collection of mathematical and statistical methods to: that evaluate relationships between a group of independent variables and one or more responses. Central Composite Design (CCD) is one of RSM and is a model of second degree with several variables, it is easy to implement and has the property of sequentiality. We can undertake the study of the first k factors while reserving the option to add new without losing the results of tests already carried out. The use of the CCD design is popular in research because it is an economical design. Apart from the conventional statistical methods (DOE), employing artificial intelligence based techniques prediction such as ANNs, fuzzy inference systems (FIS), genetic programming (GP), and regression trees are recently highlighted in literature (Sarve et al., 2015). Recently, ANNs are an interesting method in several Artificial Neural Networks:, it is one of the important artificial intelligence tools which can be used to solve problems that are not eligible for conventional statistical methods (Shojaeimehr et al., 2014). Some researchers tried to develop an evaluation of RSM and ANNs as two useful methods to predict and simulate recovery of phenolic compounds using conventional processes from Garcinia mangostana (Cheok et al., 2012), and efficient extraction of artemisinin from Artemisia annua (Pilkington et al., 2014).

Therefore, in the present investigation, a two level three factor (2^3) full factorial central composite design (CCD) in RSM and an ANN based model were developed and compared to indicate how the percentage of TPC recovery, through the green extraction process of *P. lentiscus* leaves, might be optimized. The experimental variables including ethanol proportion, amplitude intensity and extraction duration, in an extraction procedure which is considered to approximate the industrial application. The developed models were then compared in their suitability for predicting TPC recovery by analysing their coefficient of determination (R^2), adjusted coefficient of determination (R^2adj), root mean square error (RMSE), mean square error (*MSE*), absolute average deviation (AAD), Mean Absolute Error (MAE), relative percent deviation (RDP) and standard error of prediction (SEP) from experimental data. The models were then used to determine the effect of the extraction conditions on TPC recovery, thereby providing an indication of the optimal conditions. Finally, the optimal solutions offered by RSM and ANN were statistically compared to the experimental values by using a paired *t*-test. To the best of our knowledge, this is the first report comparing RSM and ANN with several statistical parameters, in natural phenolic ultrasound extraction technology from *P. lentiscus* leaves.

2. Materials and methods

2.1. Plant materials

The leaves of *P. lentiscus* were harvested in June 2012 from spontaneous plants in Oued Ghir, Bejaia, located in the North East of Algeria. The collected samples were identified by the Veg-etable Ecological Laboratory of the Algiers University, Algeria. The samples were washed with tap water followed by distilled water, dried in a static oven at 40 °C for about one week, and then ground in an electrical grinder (IKA model A_{11}Basic) to obtain fine powder. Then, the powder was passed through standard 125 μm sieve and stored in airtight bags under darkness until use. Moisture content was assessed by constant weight at 105 °C and was 5.0 ± 0.5 %, the water activity A_w (HygroPalm A_w) was 0.18 ± 0.2 at 20.6 °C.

Table 1
The experimental design layout and corresponding responses for Central composite design (CCD) based on response surface methodology (RSM) and artificial neural network (ANN) and predicted values for yield of total phenolic compounds from *P. lentiscus* leaves (TPC) using ultrasound assisted extraction (UAE). GAE, gallic acid equivalents; referred to dry weight (dw).

Run	X_1-Time	X_2-Amplitude	X_3-Solvent	Experimental	TPC yield (mg_{GAE}/g_{dw})			
					Predicted		Residual	
					RSM	ANN	RSM	ANN
1	5	30	30	138.39	139.55	138.55	−1.16	−0.16
2	15	30	30	139.79	140.96	139.85	−1.17	−0.06
3	5	70	30	163.41	160.37	163.42	3.04	−0.01
4	15	70	30	110.57	108.78	110.48	1.78	−0.09
5	5	30	70	63.33	66.98	63.48	−3.65	−0.15
6	15	30	70	109.18	114.07	109.02	−4.89	0.16
7	5	70	70	157.51	158.20	157.66	−0.69	−0.15
8	15	70	70	151.60	152.29	152.30	−0.69	−0.70
9	10	50	50	142.46	143.49	142.25	−1.03	0.21
10	10	50	50	141.55	143.49	142.25	−1.94	−0.7
11	10	50	50	142.08	143.49	142.25	−1.41	−0.17
12	10	50	50	144.11	143.49	142.25	0.62	1.86
13	17.05	50	50	146.32	143.57	145.68	2.75	0.64
14	2.95	50	50	147.72	146.74	147.37	0.98	0.35
15	10	78.2	50	146.32	149.53	142.26	−3.21	4.06
16	10	21.8	50	114.85	107.90	114.96	6.95	−0.11
17	10	50	78.2	126.10	119.83	126.01	6.27	−0.09
18	10	50	21.8	137.77	140.31	138.01	−2.54	−0.24

2.2. Extraction and quantification of TPC

2.2.1. Ultrasound assisted extraction

The extraction of phenolic compounds originating from *P. lentiscus* leaves by means of ultrasound was performed according to the CCD matrix model. A CCD consists of three sections including the full factorial design points (where the factor levels are coded to the upper level that corresponds to +1 and the lower level to −1 values), axial points (sometimes called "star"points, where the factor levels are coded to the upper level that corresponds to + α and the lower level to - α values) and the central point that can be replicated to provide an estimation of experimental error variance (Hafizi et al., 2013a) (see details below, Section 2.4). According to the DOE model, the UAE was performed at different ultrasound power of the transducer (21.8–78.2%), extraction duration (2.5–17.5 min) and ethanol proportion (21.8–78.2%) at room temperature which were controlled by circulation of a cold water (25 ± 2 °C) using thermostatic pump (Table 1). Ultrasonic irradiation was applied by means of a UP-200S sonifier (200 W, 24 kHz) (Hielscher Ultrasonics, Teltow, Germany). The extract was filtered through a Whatman No. 1 (⊘ 0.45 μm) filter paper under vacuum pump and the filtrate was then diluted to the final volume of 50 mL and was used for analysis.

After DOE–CCD-RSM and ANN optimization methods, the extraction of *P. lentiscus* leaves powder was done under optimized operational conditions. One grams of leaves powder were extracted with 40 mL of 30.99 % ethanol, amplitude intensity of 33.82 during 13.79 min. Then the final volume of the extract was completed to to 50 mL with the extraction solvent and was used for further analysis.

2.2.2. Accelerated solvent extraction (ASE) procedure

Extraction of the pistacia leave materials was carried out using accelerated solvent extractor (ASE, Dionex Corp., Sunnyvale, CA) system. The leave powder (1 g) was placed in two layers of diatomaceous earth (about 0.5 g in each layer) in 11 mL Dionex (ASE 200) stainless-steel cell, and extracted with ethanol 40%. The cells were equipped with a stainless steel frit and a cellulose filter (Dionex Corp.) at the bottom to avoid the collection of suspended particles in the collection vial. A dispersing agent (diatomaceous earth), was used to reduce the solvent volume used for the extraction. The extraction was performed at 1500 psi and optimal temperature (120 °C), and then heated for 6 min, followed by a three static periods of 5 min (3 static cycles). The sample was flushed with 70 % and purged with a flow of nitrogen during 90 s. Extracts (25 mL) were collected into 50 mL tubes. The extract was then recovered and analysed as reported in Section 2.3.1 for the optimized UAE extract.

2.2.3. Conventional extraction

For the conventional solvent extraction, 1 g of fine powder was placed in a conical flask of 250 mL (Ø × H: 51 × 150 mm and cap size of 38 mm), and 50 mL of 40 % (v/v) EtOH were added. The mixture was kept in a thermostatic water bath (mod. WNB22, Memmert) with shaking speed of 110 strokes per minute, at 60 °C for 2 h, according to the method recommended by Spigno et al. (2007). The extract was then recovered and analysed as reported in Section 2.3.1 for the optimized UAE extract.

2.2.4. Determination of polyphenol content

The content in TPC of the *P. lentiscus* leaves extract was determined by Folin's assay as reported in literature (Jaramillo-Flores et al., 2003). Briefly, 100 μL of the extract was mixed with 750 μL Folin–Ciocalteu diluted reagent (1/10). Then, the solutions were mixed and left at room at room temperature for 5 min. After that, 750 μL of 7.5 % sodium carbonate (Na_2CO_3) solution was added. After incubation at 25 °C for 90 min the absorbance was measured at 725 nm (1 cm optical path) against a blank (made as reported for the sample but with 100 μL of sample solvent) using a Spectro Scan 50 UV–vis spectrophotometer. Gallic acid hydrate was used as standard for the calibration curve to express the TPC concentration of the sample as mg L^{-1} of gallic acid equivalents (GAE). TPC yield was then calculated based on the sample concentration, extract volume and leaves powder dry weight, according to the following equation (Eq. (1)):

$$\text{TPyield} = \frac{\frac{mg_{GAE}}{L \times L_{Extract}}}{g_{dw\ leaves\ powder}} \quad (1)$$

2.3. Antioxidant power–scavenging effect

2.3.1. Scavenging activity against DPPH• radical

The free radical scavenging ability of the extract was measured using a colorimetric method where change in the purple colour solution of DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical was mea-

sured on a plate reader (Omega FLUOstar, BMG Labtech, Cary, NC, USA). 300 μL of DPPH• solution in methanol (70 μM) was mixed with 10 μL of extract and the mixture was incubated for 20 min at 37 °C. The decrease in absorbance reading of the mixture was measured at 515 nm. The antioxidant capacity of the extract was expressed as a percentage of inhibition of DPPH radical (% inhibition of DPPH radical) calculated according to the following equation (Eq. (2)):

$$\%\text{inhibition} = \text{AOX} = \frac{A_{\text{blank}_{t-20}} A_{\text{sample}_{t-20}}}{A_{\text{DPPH}_{t-0}}} \quad (2)$$

where, A_{blank} is the absorbance value of the blank (300 μL of DPPH solution plus 10 μL of the solvent in which the extract has been dissolved); A_{sample}, is the absorbance of the sample extract; t is the time (min) at which absorbance was read and A_{DPPH} is absorbance of the control at time = 0 min. The effective concentration of sample required to scavenge DPPH radical by 50 % (IC_{50} value) is obtained by linear regression analysis of dose–response curve plotting between% inhibition and concentrations.

2.3.2. Oxygen radical absorbance capacity (ORAC) assay

The antioxidant capacity of the extract was also performed using an oxygen radical absorbance capacity (ORAC) assay using a fluorescence plate reader following the procedures of Huang et al. (2002) with slight modifications. The plate reader was equipped with an incubator and two injection pumps. Briefly, sample extracts of 20 μL with suitable dilution in phosphate buffer saline solution (75 mM, pH 7.0) were loaded to polystyrene 96-well microplates in triplicate based on a randomised set layout.

The samples were diluted to the proper concentration range for fitting the linearity range of the standard curve. After loading 20 μL of sample, standard and blank, and 200 μL of the fluorescein solution into appointed wells according to the layout, the microplate (sealed with film) was incubated for 15 min in the plate reader at 37 °C and then 20 μL of peroxyl generator 2,2′-azobis(2-amidinopropane dihydrochloride (AAPH) (3.2 μM) was added to initiate the oxidation reaction. The plate reader was programmed to inject and record the fluorescence of fluorescein on every cycle. The kinetic reading decrease of Fluorescein intensity (%) was recorded for 60 cycles with 40 s per cycle setting during 40 min at 37 °C. Absorbance readings of the plate were taken every cycle using an excitation wavelength of 485 nm and an emission wavelength of 535 nm until all fluorescence readings declined to less than 25% of the initial values.

Four Trolox solutions (6.25, 12.5, 25, 50 μM in phosphate buffer saline solution (75 mM, pH 7.0) were used to establish a standard curve.

The area under the curve (AUC) was calculated for each sample by integrating the relative fluorescence curve (Eq. (3)).

$$\text{AUC} = \left(0.5 + \frac{f_4}{f_3} + \frac{f_5}{f_3} + \frac{f_6}{f_3} + \ldots + \frac{f_i}{f_3}\right) \times \text{CT} \quad (3)$$

where f_3 is the initial fluorescence reading at cycle 3, fi is a fluorescence reading at cycle i, and CT is cycle time in minutes. The net AUC of the sample was calculated by subtracting the AUC of the blank.

The regression equation between net AUC and Trolox concentrations was determined and ORAC values were expressed as μmol Trolox equivalents per gram of sample (μmol TE g^{-1}) using the standard curve established in the same conditions (R^2 = 0.9946).

2.4. Mathematical models

2.4.1. Central composite design (CCD)

The effects of extraction processing variables on phenolic contents including ethanol proportion, extraction time and extraction amplitude were investigated by the one-variable-at-a-time method (preliminary study). On the basis of the single factor experimental results, major influent variables were confirmed, and then a response surface methodology was conducted to design experimental project. JMP software package was used to establish a CCD-RSM mathematical model and obtain the optimum conditions of the green ultrasound technology.

The CCD consist of:

- Full Factorial Design (FFD) with two levels (n_f) (coded values ± 1): $n_f = 2^k$, where k is the number of factors (three variables in this work) (Table 1);
- Central points, could be a function of the experimenter and have the coordinates n_0 (coded values 0). These experiments are used to assess the repeatability, they are used to ensure that there is no slip between the FFD and star plan, they are involved in the calculation of α, these points provide also a mean for estimation of the experimental error and provide a measure of lack-of-fit and finally they are used to test the validity of the model (Table 1);
- The "star points" ($n\alpha = 2k$) (coded values ± α), add two more levels in each k variable (Table 1). The total number (n) of the CCD to be performed is (Eq. (4)):

$$n_{\text{totaloftest}} = n_f + n_\alpha + n_0 \quad (4)$$

The α value is calculated to obtain a near-orthogonality. Frequently the value of α is selected to make the rotatable design and is satisfied as follow (Eq. (5)):

$$\alpha = \left(\frac{n_f \left(\sqrt{n_0 + n_f + n_\alpha} - \sqrt{n_f} \right)^2}{4} \right)^{\frac{1}{4}} \quad (5)$$

The variables were coded according to the following equation (Eq. (6)):

$$xi = \frac{X_i - X_0}{\Delta X} \quad (6)$$

where $X_i$is the (dimensionless) coded value of the variableX_i, $X_0$is the value of X at the center point and ΔX is the step change.

The experiment design is shown in Table 1, along with experimental data. The extraction rate of TPPL is the response. The regression analysis was performed to estimate the response function as a second-order polynomial, the variables were coded according to the following equation (Eq. (7)):

$$Y_{\text{TPPL}} = B_0 + \sum_{i=1}^{k} B_i X_i + \sum_{i=1}^{k} B_{ii} X^2 + \sum_{ij}^{k} B_{ij} X_i X_j + E \quad (7)$$

where, Y_{TPPL} represented the response function of total phenolic from Pistacia leaves (TPPL). B_0 was constant coefficient. B_i, B_{ii} and B_{ij} were the coefficients of the linear, quadratic and interactive terms, respectively. According to the standard least square methods and analysis of variance, the regression coefficients of individual linear, quadratic and interaction terms were determined. In order to visualize the relationship between the response and experimental levels of each processing variable and to deduce the optimum conditions, the regression coefficients were then used to make statistical calculation to generate 3-D surface plots from the fitted polynomial equation. The P-values of less than 0.05, 0.01 and 0.001 were considered to be statistically significant.

The determination coefficient (R^2), adjusted coefficient (R^2 adj), the root mean-squar-error (RMSE), adequation precesion (Adeq prec) of the function were used for evaluating the statistical significance of the model developed (Table 2).

Table 2
Analysis of variance (ANOVA) for the experimental results obtained by using ultrasound assisted extraction.

Source	Sum of squares	DF***	*F*-value	*P*-value Prob>F
Model	8832.36	9	47.33	<0.0001
X_1-Time	9.02	1	0.43	0.5306
X_2-Amplitude	2585.17	1	124.67	<0.0001
X_3-Ethanol	620.26	1	29.91	0.0009
X_1X_2	1424.97	1	68.72	<0.0001
X_1X_3	1061.45	1	51.19	0.0002
X_2X_3	2451.05	1	118.2	<0.0001
X_1^2	19.63	1	0.94	0.363
X_2^2	371.52	1	17.91	0.0039
X_3^2	303.52	1	14.63	0.0065
Residual	145.14	8		
Lack of Fit	142.67	5	23.06	0.0421
Pure Error	2.47	3		
R^2	0.98			
R^2adj	0.96			
Adeq pre*	26.25			
RMSE**	4.65			
Cor Total	9165.69	18		

* Adequation precision.
** Root mean square error.
*** Degree of freedom.

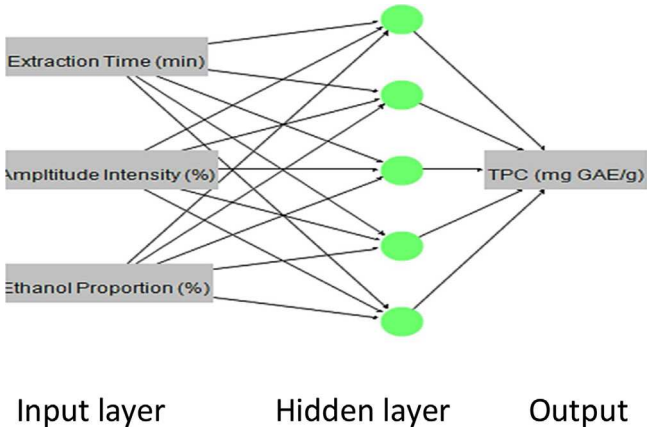

Fig. 1. ANN design for three operating parameters (irradiation time (X_1); Amplitude (X_2) and ethanol proportion (X_3)) as input, and TPC yield as output.

2.4.2. *Artificial neural network artificial (ANN)*

Artificial neural networks (ANNs) are mathematical models, which were inspired from the functioning of biological nervous systems and come from Artificial Intelligence, have proved to be a powerful modeling technique for complex and nonlinear problems with strong proposed to learning and function approximation (Hafizi et al., 2013b). The experimental data on the recovery of phenolic compounds obtained by UAE method was used for training the ANN and it was developed in JMP. A multilayer perceptron (MLP) is a feed-forward ANN consisting three or more layers of neurons, with the first layer of neurons representing the independent parameter inputs (Fig. 1). Each of the neurons in the first layer is connected to one or more layers of hidden neurons that represent nonlinear activation functions (Pilkington et al., 2014). These neurons are inturn connected to a final level of output neurons and, through these of learning algorithms, the relative influence of each input neuron and their complex interactions on the observed result can be discerned (Pilkington et al., 2014). The inputs to the ANN model were identical to the factors considered in RSM approach, namely extraction time, amplitude and ethanol proportion, a single hidden layer of neurons, and an output neuron representing the recovery of total phenolic compounds, was a similar to RSM modeling (Y_{TPC}. A representation of the MLP architecture can be observed in Fig. 1. The number of hidden neurons required in the hidden layer was determined by trial and error to minimise the deviation of predictions from experimental results planned through CCD. A total of 18 of experimental results were used to train the network, with the remaining results split evenly between network validation and testing (Table 1). In our case, K-Fold cross-validation procedure was used for the validation and testing of ANN-model, consisting on dividing the original data into K subsets. In turn, each of the K sets is used to validate the model fit on the rest of the data, fitting a total of K models. The model giving the best validation statistic is chosen as the final model (Table 3). This method is the best for small data sets, because it makes efficient use of limited amounts of data. The ANN predictions were then used to generate surface plots.

The determination coefficient (R^2), the root mean-squar-error (RMSE), Log likelihood test, Mean Absolute Deviation (MAD) and sum of squar error (SSE) of the function were used for evaluating the statistical significance of the the ANNs models developed (Table 3).

2.5. *Statistical analysis*

The statistical software package JMP (10.0.0 version, SAS Institute) was used for a regression analysis of experimental data, plotting the response surfaces and analysis of variance (ANOVA) of the statistical parameters for TPC recoveries.

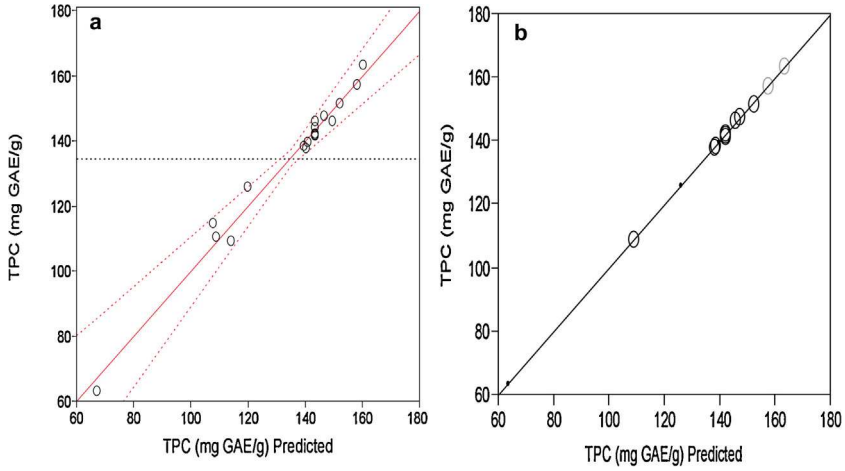

Fig. 2. Comparison between experimental and predicted values of UAE content for RSM (a) and ANN (b) models.

Table 3
Performance of ANN training and ANN validation models.

TPC (mg_{GAE}/g_{dw})	
Training	
R^2	0.999741
RMSE*	0.3722593
MAD**	0.2902812
-Log Likelihood test	6.4616106
SSE***	2.0786553
Sum Freq	15
Validation	
R^2	0.9948071
RMSE	1.0740733
MAD**	0.6852675
-LogLikelihood	4.4711903
SSE***	3.4609004

Table 4
Comparison of the performance of response surface methodology and artificial neural networks.

Performance equations	RSM	ANN
$R^2 = \frac{\sum_{i=1}^{N}(X_i - Y_i)^2}{\sum_{i=1}^{N}\left(\bar{Y}_i - Y_i\right)^2}$	0.981	0.999
$R^2\text{Adj} = 1 - \left[\left(1 - R^2\right) \times \frac{N-1}{N-k-1}\right]$	0.967	0.999
$\text{SEP} = \frac{\text{RMSE}}{Y_e} \times 100$	3.45	0.28
$\text{MAE} = \sum_{i=1}^{N}\left(\frac{Y_{i,\text{exp}} - Y_{i,\text{pred}}}{N}\right)$	0.0006	0.26
$\text{AAD} = \left(\frac{1}{N}\sum_{i=1}^{N}\left(\frac{Y_{i,\text{pred}} - Y_{i,\text{exp}}}{Y_{i,\text{exp}}}\right)\right) \times 100$	0.14	0.18
$\text{RDP} = \frac{100}{N}\sum_{i=1}^{N}\frac{\left\lvert\left(Y_{i,\text{pred}} - Y_{i,\text{exp}}\right)\right\rvert}{Y_{i,\text{exp}}}$	0.103	0.022
$\text{MSE} = \frac{\sum_{i=1}^{N}(Y_{i,\text{exp}} - Y_{i,\text{pred}})^2}{N}$	9.63	1.21
$\text{RMSE} = \sqrt{\frac{\sum_{i=1}^{N}(Y_{i,\text{exp}} - Y_{i,\text{pred}})^2}{N}}$	4.65	0.37

MSE, mean squared error; RMSE, root mean square error; AAD, absolute average deviation; MAE, mean absolute error; RDP, relative percent deviation; SEP, standard error of prediction.

Influence of extraction technique (UAE, ASE or CSE) on TPC yield and extract AOC was assessed by univariate ANOVA and Tukey's post hoc test for means discrimination (95 % confidence level).

In addition, to evaluate the goodness of fit and prediction accuracy of the constructed models, correlation coefficients (R^2), adjusted determination coefficient (R^2adj), root mean square error (RMSE), Mean Squared Error (MSE), Mean Absolute Error (MAE) and absolute average deviation (AAD), relative percent deviation (RDP), standard error of prediction (SEP) were carried out between experimental and predicted data (Table 4) (Rafigh et al., 2014; Sarve et al., 2015).

3. Results and discussion

3.1. Modeling and optimization using CCD–RSM of extraction process

According to the CCD, experiments were performed in order to find out the optimum combination conditions and study the effect of process parameters on TPC recovery using the ultrasound process, and the results are given in Table 1. In the present work, there were a total of 18 runs for optimizing the three processing parameters. By applying multiple regression analysis on the experimental data, the mathematical model representing the recovery of TPC_{UAE} within the levels under investigation was expressed by the second-order polynomial Eq. (8) using the standard least squar (LSM) method with actual factors:

$$Y_1 = 149.02 + 1.63X_2 - 2.11X_3 - 0.13X_1X_2 + 0.13X_1X_3 + 0.043X_2X_3 - 0.02X_2^2 - 0.01X_3^2 \quad (8)$$

Table 2 shows the result of analysis of variance for the fitting model. Values of probability (P)>F less than 0.05 and 0.01 indicate that model terms are significant and highly significant respectively, and the values greater than 0.05 indicate that the model terms are not significant. From the Table 2, the ANOVA reveals that the model was highly significant with a p-value < 0.0001, which means that the model represented the data satisfactorily. In other ways, 98.12 % of the variations could be covered by the fitted model. Furthermore, the values of pure error 2.47 is low which indicate good reproducibility of the data. The coefficients of determination (R^2) and adjusted coefficients (R^2 Adj) are close to 1, which revealed also, that there are excellent correlations between the predicted and experimental models (Fig. 2a). In addition, the small values of CV (3.45 %) than 10 and higher values of adequate precision than 4 for both extraction plants give better reproducibility and adequate signal (Table 2). Moreover, "The ¨Pred R-Squared"öf 0.8422 is in reasonable agreement with the ¨Adj R-Squared"öf 0.9630;ï.e. the difference is less than 0.2. In conclusion, these models can be used to navigate the design space.

3.2. Response surface analysis

The interactions among different process parameters and optimum identifying values for reaching the maximum recovery were investigated by a 3D surface plot according to Eq. (8).

The plots were designed by sketching the response (z-axis) versus two output independent variables (x and y coordinates) and the other independent variables were considered constant at their zero levels of the testing ranges (Ghoreishi and Heidari, 2013). The recovery of TPC mainly depends on the extraction time, amplitude and ethanol proportion as its linear effect for amplitude and ethanol proportion and all mutual effects were highly significant at $p < 0.01$ (Table 2). The P-values at 0.05 and 0.01 were used as a tool to check the significance or highly significance of each coefficient. It can be seen from Table 2 that, the linear coefficients (X_2, X_3) a quadratic term coefficient ($X_2{}^2, X_3{}^2$) and cross product coefficients (X_1X_2, X_1X_3, X_2X_3) (Fig. 3), were highly significant, with very small P-values ($P < 0.01$). The other term coefficients were not significant ($P > 0.05$).

In Fig. 4A, when the 3-D response surface plot was developed for the extraction yield of TPC with varying extraction time and output amplitude at fixed extraction solvent (0 level), the extraction yield of phenolic content increased with the increasing extraction time (2.5–17.5 min), and and was enhanced rapidly with increase of output amplitude from about 30–78 % over investigated range (Fig. 3). It can be seen from Table 2 that, the cross effect of time-amplitude (X1 × 2) was highly significant, with very small p-values ($P < 0.0001$). The intensification of extraction process has been attributed to the physical effects of ultrasound such as a cavitation which can lead to a significant increase in the mass transfer rates. Ultrasound can be effectively used to increase the yield and rate of mass transfer in several solid–liquid extraction processes. Similar results obtained by Kadam et al. (2015) also showed that ultrasonication could increase the recovery of bioactive compounds from *Ascophyllum nodosum* materials.

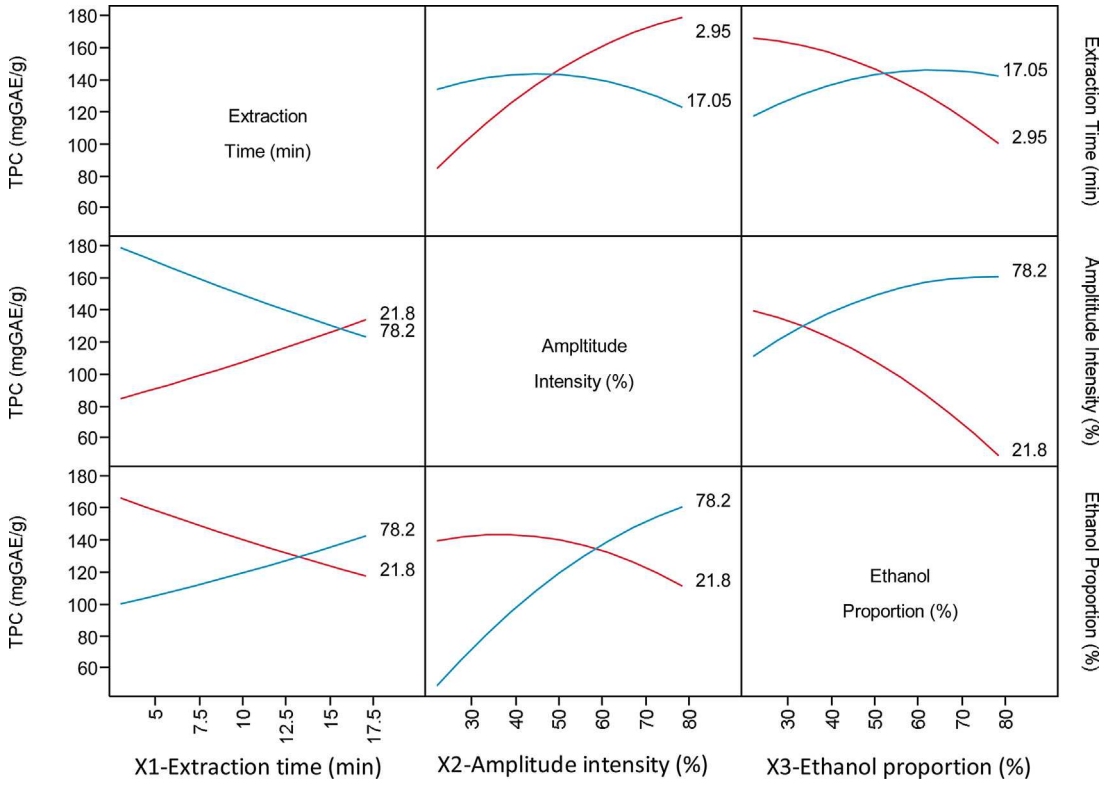

Fig. 3. Interaction plots of the processing variables (to irradiation time (X_1); Amplitude (X_2) and ethanol proportion (X_3)) on the recovery of TPC. The interaction shows as nonparallel lines. Red lines display factor at low level, whereas blue lines are the high level of the factors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 4B depicts the extraction yield of TPC as a function of extraction time and aqueous ethanol at fixed output amplitude (0 level or 50 %), it indicated that the maximum extraction recovery of TPC can be achieved when extraction time and ethanol proportion are at the levels of 2.5 min and 20 %, respectively (Fig. 3). It is clear that the interaction between these investigated variabes is highly significant with $p < 0.0002$. In fact, in ultrasound process, a cavitation phenomena produced at high amount of water (80 %, low purity of extraction solvent) is one of the key variables affecting the release of polyphenols from different matrices by violent cavitation collapsing bubbles, which have the ability to modify equilibrium and mass transfer conditions during extraction. Due to cavitation, the cracks are developed in the cell wall which increases permeability of plant tissues facilitating the entry of the solvent into the inner part of the material as well as washing out of the extracts (Rodrigues et al., 2015). Exposure of polyphenols to the ultrasonic waves for a longer period beyond about 5 min results in the structural destruction, which results in a reduced yield. In addition, increasing radiation time in all reactions, including the formation of free radicals which can be scavenged by phenolic compounds (Jerman et al., 2010), are promoted when high times/amplitudes are used.

The effect of mutual interaction between output amplitude and ethanol proportion is shown in Fig. 4C and was higly significant ($p < 0.0001$) with a maximum TPC yield at 78 % ethanol proportion and 78 % amplitude (Fig. 3). Results indicated that extraction of active compounds from the plant materials were accomplished after 10 min. Increase in the ethanol proportion required high sonication intensity to generate the cavitation bubbles. It is know that the cavitation phenomena is favorated by the degree of impurities in the medium. The cavitation bubbles is mainly medium nature dependent.

In conclusion, the optimum of TPC recovery of 140.55 mg GAE g^{-1} was obtained via the canonical analysis of response surface which predicted the following conditions as 13.79 min extraction time, 33.82 % amplitude and 30.99 % ethanol proportion. The accuracy of the modeling optimal TPC recovery was validated with triplicate experiments giving the average extraction recovery of 142.76 ± 19.98 mg GAE g^{-1}.

3.3. Artificial neural network model

The recovery of TPC as predicted by the ANN is compared to the experimentally obtained values in Table 1. In order to test the suitability of the model, the predicted and actual results were plotted in Fig. 2b.

By supplying the ANN model with matrices of extraction condition parameters, it was possible to visualise the relative impact of each extraction variables using surface plot generated in JMP (Fig. 5). Using the same approach as with the RSM model, the third variable for each plot was fixed at its middle value (10 min, 50 % or 50 %) to generate the surface plots and the results of this investigation can be observed in Fig. 5. It is directly obvious from Fig. 5A that, increasing the ultrasound intensity from 20 % (code = −1) to 70 % (code = +1) improve the recovery of phenolic content and this leads to higher internal mass transfer and consequently enhanced the TPC extraction recovery. Extraction amplitude has a significant effect on the recovery efficiency of TPC as a state of equilibrium has been attained at the high amplitude. In this circumstance (with ethanol 50%), the only way to increase the extraction of polyphenols is to increase the ultrasonication intensity of extraction, which is in line with the increasing solubility of phenolic compounds in extraction solvents with increasing irradiation intensity. The results in Fig. 5B, indicate that the interaction effect of extraction duration and ethanol proportion is inversement proportional to the recovery of TPC, which suggests that the extraction has run to completion at 30 % of ethanol for about 5 min and that higher TPC recovery

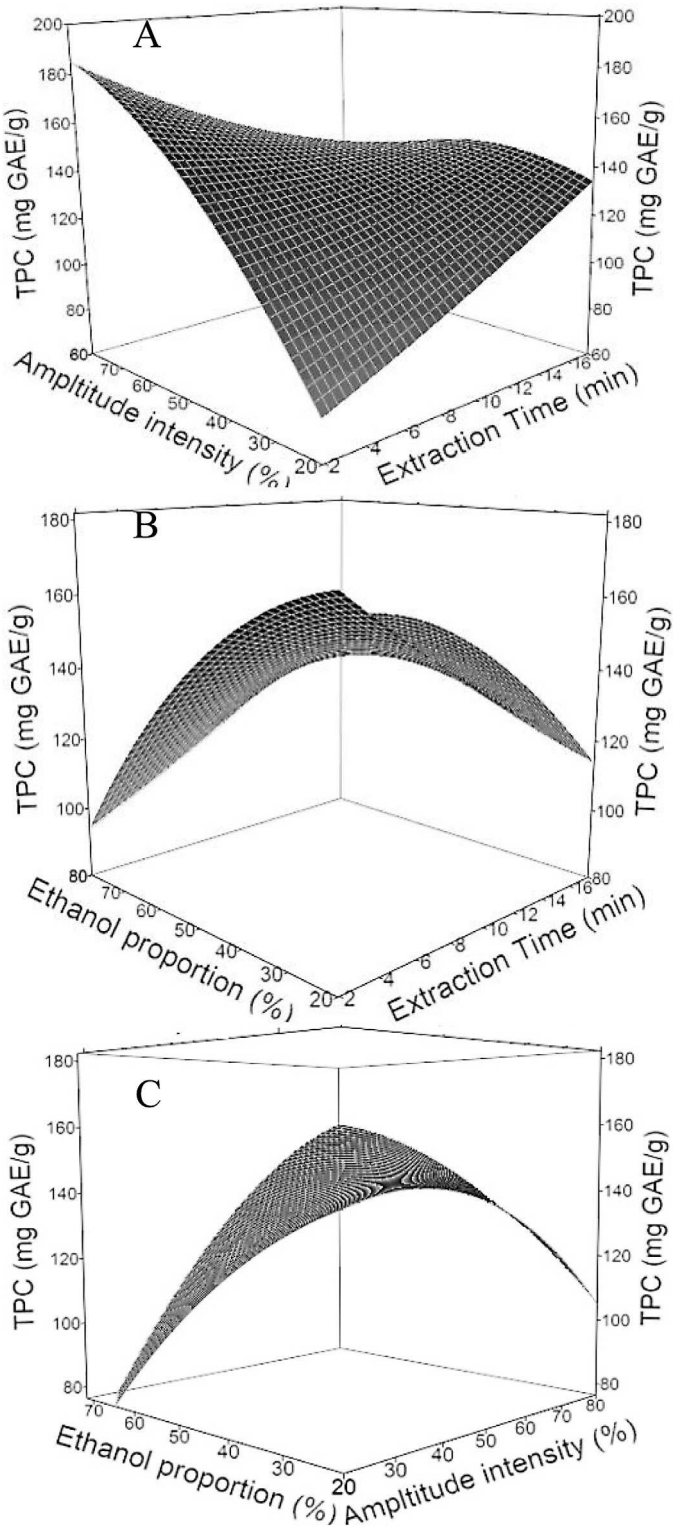

Fig. 4. Response surface analysis for the total phenolic yield from *P. lentiscus* leaves with ultrasound assisted extraction method with respect to irradiation time (X_1); Amplitude (X_2) and ethanol proportion (X_3), according to the RSM model.

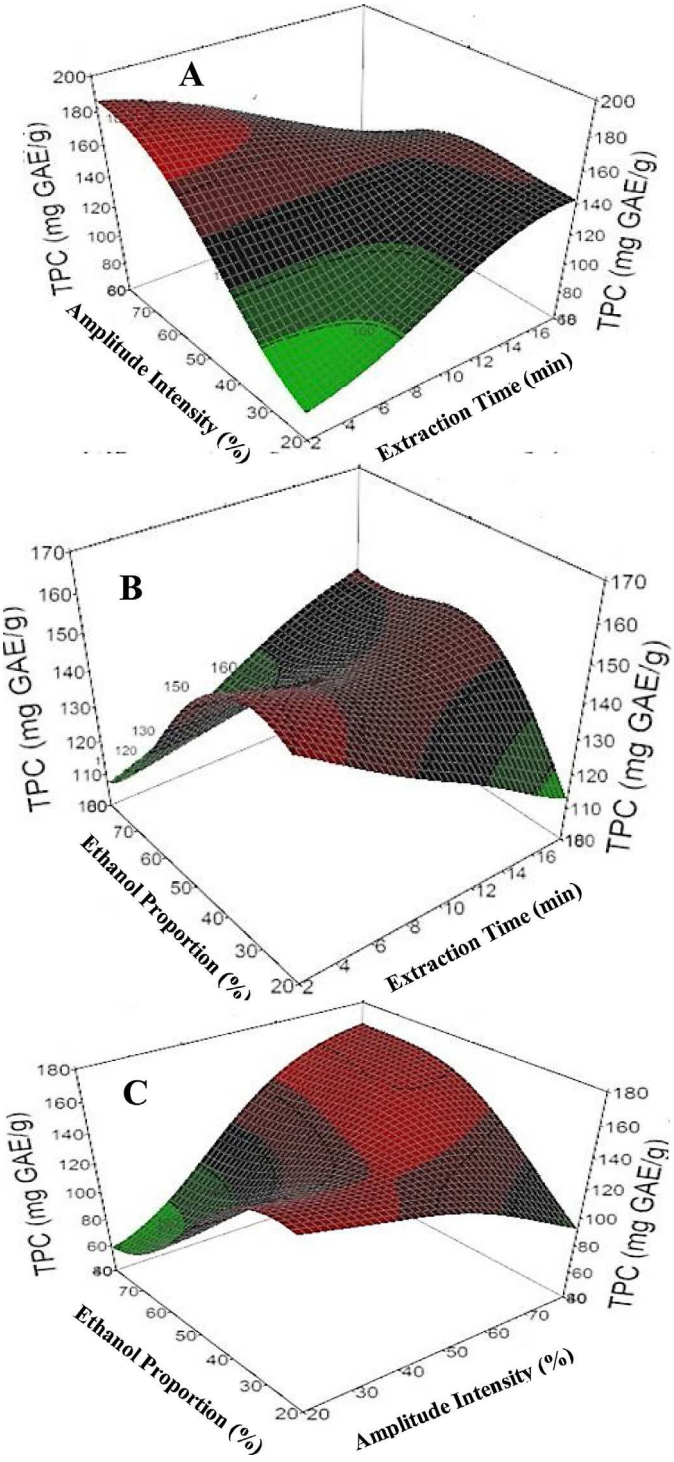

Fig. 5. Response surface analysis for the total phenolic yield from *P. lentiscus* leaves with ultrasound assisted extraction method with respect to irradiation time (X_1); Amplitude (X_2) and ethanol proportion (X_3), according to the ANN model.

could only be obtained by reducing the concentration of ethanol proportion and time.

The results in Fig. 3C indicate an usual trend at higher ethanol proportion in water, particularly beyond 60 %, the higher energy of ultrasonication required. This explained by the fact that the extraction of TPC from vegetable tissue material requires more energy intensity, when high percentage of pure solvent is used to generate to generate a cavitation phenomena. This is an important observation as it suggests that proportion of solvent in water extractions with high purity may be able to retard a cavitation in terms of extraction efficiency. As well as cost savings by running the extraction at lower proportion of organic solvents in water, there is the potential that the extraction of certain impurities (as chlorophyll, fibers, ...) may be reduced, leading to a cleaner extract to be taken forward for purification.

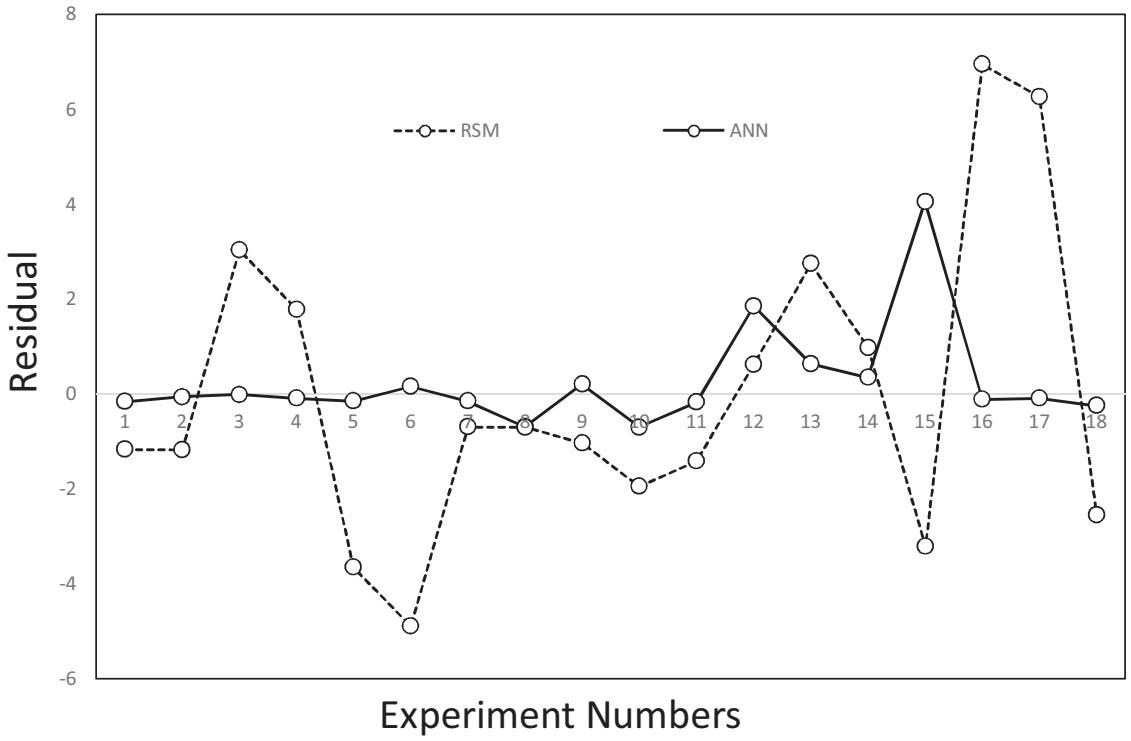

Fig. 6. Comparison between the residual errors obtained by RSM (a) and ANN (b) models.

It is hypothesized that a critical concentration of ethanol proportion is attained at about 40 % and that the solubility of TPC is sufficiently improved in the extraction mixture as to promote increased recovery from the Pistacia leaves.

3.4. Validation and comparison of RSM and ANN models

In the last decades, response surface methodology (RSM) and artificial neural network (ANN**s**) has become the most preferred methods for machining (Kumar and Chauhan, 2015).

In this present work, RSM and ANN methods were applied for modeling and optimization of ultrasound-assisted extraction of phenolic natural compounds from *P. lentiscus* leaves. In order to validate the adequacy of the mathematical models, a verification experiment combination factors was carried out under the optimal conditions. Under these optimal conditions, RSM and ANN models predicted a maximum response of 140.55 and 138.34 mg GAE g^{-1}dw, respectively. A mean value of 142.76 ± 19.98 mg GAE g^{-1}dw, obtained from real experiments, demonstrated the validation of the extraction models. The good correlation between these results confirmed that the models were adequate for reflecting the expected optimization. The performance of the constructed ANN and RSM models were also statistically measured and summarized in Table 4. The determination coefficient (R^2) in RSM and ANN were given 98.6 % and 99.9 %, respectively. Thus the calculated R^2 demonstrates a superior accuracy of ANN in contrast with the traditional RSM (Fig. 5). From a Table 4, the statistical analysis of RSM and ANN models provided good quality predictions, yet the ANN showed a clear superiority over RSM for both data fitting and estimation capabilities.

The actual and predicted values together with the residuals, for both approaches are presented in Table 1. In order to compare the distribution of predicted and actual values of two approaches, the results were plotted in Fig. 6.

The fluctuations of the residuals are relatively small and regular for ANN compared to RSM. The RSM model shows greater deviation than the ANN model. It is to be noted that though RSM has the advantage of giving a regression equation for prediction and showing the effect of experimental factors and their interactions on response in comparison with ANN. ANN does not require a standard experimental design to build the model (Geyikçi et al., 2012). The ANN approach is flexible and permits to add new experimental data to build a trustable model. Thus it would be more rational and reliable to interpret ultrasound-assisted natural phenolic compounds extraction data through a process of ANN architecture.

Table 5
Comparison of extraction yield and antioxydant activities of polyphenols from *P. lentiscus* leaves by Ultrasound assisted extraction (UAE), Accelerated solvent extraction (ASE) and Conventional solvent extraction (CSE). Results are expressed as means ± standard deviation.

	Antioxydant activity		
	TPC (mg_{GAE}/g_{DW})	ORAC (μmol TE/g_{DW})	DPPH (IC_{50}) (μg_{GAE}/mL)
UAE	142.76 ± 19.98^{ab}	517.52 ± 35.18^{b}	18.74 ± 0.284^{c}
ASE	120.78 ± 16.00^{b}	257.07 ± 20.00^{c}	32.77 ± 2.12^{a}
CSE	178.00 ± 19.80^{a}	671.07 ± 58.80^{a}	19.76 ± 0.06^{b}

Same letters in the same column refer to means not statistically different ($p > 0.05$).

3.5. Comparison of UAE with ASE and traditional extraction method

One of the quick methods to evaluate antioxidant activity is the scavenging activity on DPPH, a stable free radical and widely used index. The DPPH method was evidently introduced nearly 50 years ago by Blois (Molyneux, 2004), and it is widely used to test the ability of compounds to act as free radical scavengers or hydrogen donors, and to evaluate antioxidant capacity.

Results showed that antiradical activity was methods-dependent (Fig. 7 and Table 5). From the point of view of the quality of the extracts, the DPPH test showed UAE as the best technology due to the significantly lower IC50 (19.76 ± 0.06) in comparison to ASE and CSE ($p < 0.05$).

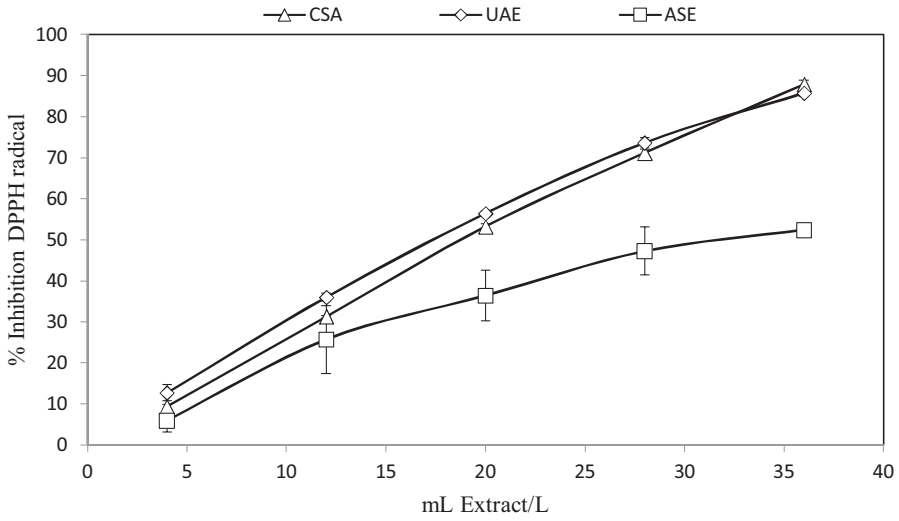

Fig. 7. Reducing capabilities of ultrasound-assisted extracted (UAE) samples compared to accelerated-solvent extraction (ASE) and conventional-solvent extraction (CSE). Reducing capacity of the extracted was quantified as% inhibition using DPPH radicals.

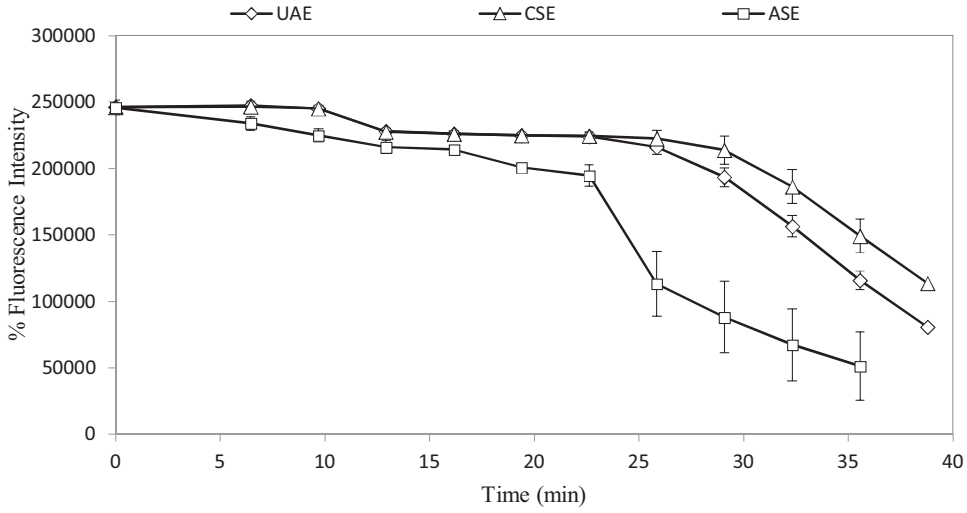

Fig. 8. Fluorescence intensity decay of ultrasound-assisted extracted (UAE) samples compared to accelerated-solvent extraction (ASE) and conventional-solvent extraction (CSE). This curve was used to determine the antioxidant activity of *P. lentiscus* extracts using ORAC assay.

From the point of view of industrial application of ultrasound technology for separation as well as for the recovery of high-added value compounds from different plant materials, it is important to know which factors influence extraction yield, but above all it is important to develop mathematical models that are able to describe and control the process.

In the ORAC assay, the different extracts showed that the antioxidant powers were statistically different for UAE, CSE and ASE using ANOVA and Turkey's post-hoc test with 95 % confidence level (Table 5). The extracts-ASE showed that the lowest antioxidant powers; the same tendency was obtained with DPPH test. Fig. 8 depicts the time course of the reaction of fluorescein with AAPH in the presence of different extracts under the conditions reported in Section 2. It is also observed that ASE-extracts have the lowest protection of fluorescence intensity during the test compared to other extraction methods, beyond 15 min the fluorescence signal was found to decline dramatically in presence of peroxyl generator (AAPH). However, by using UAE and CSE-extracts the tendency was prolonged until about 30 min (Fig. 8).

The lowest antioxidant activities of ASE-extracts can be explained by unfavorable conditions of extraction as like other techniques. ASE is considered as a potential alternative technique to conventional atmospheric pressure methods, for the extraction of naturel compounds. Compared with conventional solvent extraction, there is a dramatic decrease in the amount of solvent and extraction time required for ASE; from our point of view of industrial and/or laboratory application of ASE mechanism for extract preparation as well as for the recovery of high-added value compounds from plant materials, it is important to know which factors influence extraction yield and it is important to develop mathematical models that are able to describe and control the optimization process.

It was mentioned earlier that the TPC of extracts obtained using UAE was also similar to that found with the CSE method although there were differences in the required extraction time used in the two other procedures. In addition, the optimal extraction time required for maximum ORAC activity using UAE was just 13 min versus 120 min with CSE, we suggest here, that a longer extraction time (approximatively 10 times) could influenced negatively the recovery of bioactive compounds. The UAE process is capable of extracting more bioactive compounds in less time.

4. Conclusion

The capability of TPC extracted from pistacia leaves using aqueuse ethanol solution and the effects of processing parameters were investigated using RSM and ANN. The most important reveals from this investigation are as follows:

- The optimum conditions were found as extraction time of 13.79 min, 33.82 % amplitude and 30.99 % ethanol proportion, and the optimum TPC recovery of 140.55 mg GAE g^{-1};
- The results of ANN and RSM models based on validation data showed that RSM (R^2 = 0.986) and ANN (R^2 = 0.999) are useful and perfect methods to predict TPC by applying UAE process. It shows that ANN model is better than RSM;
- Strong antioxidant activity for UAE extract were obtained with DPPH and ORAC radicals compared to the ASE technique, UAE allows the quantitative and reproducible extraction of the phenolic compounds present in Pistacia leaves, in a short time followed by CSE;
- The research findings for UAE optimization with RSM and ANN models will provide effective guidelines and the results would be a good database to the Food-industry applications for use in health-care food;
- The leaves of *P. lentiscus* are rich in polyphenols. However, further studies concerning the nutritional and health benefits are required before a large scale utilization of the lentisc leaves can be recommended.

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