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A novel approach for olive leaf extraction through ultrasound technology : Response surface methodology versus artificial neural networks

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Abstract−Response surface methodology (RSM) and artificial neural network (ANN) were used to evaluate the ultrasound-assisted extraction (UAE) of polyphenols from olive leaves. To investigate the effects of independent parameters on total phenolic content (TPC) in olive leaves, pH (3-11), extraction time (20-60 min), temperature (30-60 ºC) and solid/solvent ratio (500 mg/10-20 mL) were selected. RSM and ANN approaches were applied to determine the best possible combinations of these parameters. Box-Behnken design model was chosen for designing the experimental conditions through RSM. The second-order polynomial models gave a satisfactory description of the experimental data. Experimental parameters and responses were used to train the multilayer feed-forward networks with MATLAB. ANN proved to have higher prediction accuracy than that of RSM.

Keywords: *Olea europaea*, Polyphenols, Ultrasound-assisted Extraction, Optimization, RSM, Box-Behnken, ANN

INTRODUCTION

Due to their natural antioxidative and antimicrobial activities, determination of polyphenols in food plants is of great significance [1-5]. These compounds are synthesized against microorganisms and UV radiation as a defense mechanism. Polyphenols are also antimicrobial, antiviral and eliminate infections [6-8]. These valuable compounds in plant extracts are responsible for many health benefits (e.g., reduction of hypertension, prevention of cardiovascular problems, and suppression of different types of cancer and viral diseases). Therefore, there is a growing interest to utilize them in various industrial applications such as food supplements, cosmetic and pharmaceutical industries [9-12]. They find application in food industry to eliminate the oxidation of lipids during processing and storage of foods. UV light, free radicals, heat, enzymes, micro-organisms and metals/metalloproteins might be the initiators of lipid oxidation. Finally, this problem gives rise to rancidity, potentially toxicoxidative products, degradation of colors, aroma, and nutritional quality, and decrease of shell life [4,13,14]. Actually, this general concern in consumer preferences towards preventing autooxidation is not restricted to the food safety. These high added value components are attractive for other industries such as pharmaceutical and cosmetic as well. Thus, these three trade sectors focus on the products known as functional food, dietary supplements, phytochemicals, and nutraceuticals [15].

Olive leaf extract has also been proven to have a potential antitolerant property against the chronic usage of morphine owing to the effect of its main component, oleuropein [16]. There is also evidence of its hypoglycemic properties, which normalizes glucose homeostasis in individuals with diabetes [17]. Recently, it has been suggested that the use of olive leaf extract could decrease breast cancer cell viability significantly by reducing the tumor growth [18]. Moreover, olive leaf aqueous extract showed antimutagenic activity as an effective procedure for preventing human cancer and genetic disease [19]. Another remarkable study presented the beneficial effects of olive leaf against obesity by regulating the expression of genes involved in adipogenesis and thermogenesis in the visceral adipose tissue of high-fat diet-fed mice [20].

A common extraction procedure cannot exist, due to the diversity in composition of phenolic compounds depending on the plant structure. Extraction methods for each bioactive compound's source must be designed and optimized. Possible interactions among process operating parameters should be considered to optimize, simulate, design and control an extraction process. Those independent parameters can be counted as extraction temperature, pressure and time, pH of the media, particle size of the extracted material, solvent type, solvent composition, and solid to solvent ratio. To optimize a process, possible interactions among other operating parameters should be considered, other than the traditional "one-factor-at-a-time" method. Response surface methodology (RSM) considers the probable interactions between operation parameters, which is a collection of statistical and mathematical techniques used for developing, improving and optimizing processes [21]. On the other hand, artificial neural networks (ANN) are data processing models produced with various mathematical and electrical methods based on the physiological structure of the brain. Due to the the parallelism, learning and adaptive features of ANN, it has found widespread application as a data processing system. ANN is a data processing system that is not algorithmic and numerical but capable of parallel processing. In brief, ANNs are interconnected artificial neural cells [22]. Razbani and Assadi [23] obtained a model by using data from the experiments with a fuel cell in ANN and predicted the voltage-

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temperature profile of the fuel cell with the obtained model. Bastani et al. [24] predicted the CO_2 absorption capacities of chemical absorbents using ANN. Doherty et al. [25] used ANN to model dynamics of non-linear pH operations. Dirion et al. [26] applied ANN to control chemical reactions. To the best of our knowledge, there is no research study comparing RSM and ANN in olive leaf extraction rich in polyphenol through UAE.

MATERIALS AND METHODS

1. Materials

Olive tree leaves were picked randomly from the same tree grown in Bursa, Turkey. After the leaves were dried, they were stored at ambient temperature in the dark and ground into particles whose average diameters were between 0.9-2.00 mm.

All chemicals used in experiments were analytical grade. Folin-Ciocalteu reagent, sodium carbonate and gallic acid, hydrochloric acid and sodium hydroxide were purchased from Sigma-Aldrich. 18 mΩ deionized water from a Millipore Milli-Q water purification system was used as solvent.

2. Ultrasound-assisted Extraction

Ultrasound-assisted extraction was conducted with ultrasonic bath (Protech, 40 kHz). Mettler Toledo SevenEasy pH meter was used to control desired pH values of solvent. Hydrochloric acid, water and sodium hydroxide were used to adjust pH levels at 3, 7 and 11. 500 mg of dried and ground plants and solvent were sealed in an Erlenmeyer flask and placed into the bath. Then, the mixture was centrifuged (Nüve, CN 180) at 5,000 ×*g* for 25 min. After centrifugation, the supernatant was filtered through a 0.45 μm syringe filter and stored at −80 °C until analysis for the biochemical measurements.

3. Determination of Total Phenolic Content

The concentration of total phenols in the extracts was measured by UV-spectrophotometry (PG Instruments, T60), based on colorimetric oxidation/reduction reaction. The total phenolic content was determined according to the Folin-Ciocalteu method by following the procedure of Malik and Bradford [27]. The amount of total phenolic content was expressed in gallic acid equivalent per *g* of dried matter (mg-GAE/g-DM).

4. Box-Behnken Design

Box-Behnken design (1960) uses three levels (−1, 0, +1) for each factor. While two of the factors are kept constant at level 0, the remaining factors are iterated within the levels +1 and −1. This process is then repeated for different groups [28,29]. In this study, Box-Behnken design was performed with four variables to explore the effect of variables on the responses. Those variables were X_1 (pH), X_2 (solid/solvent ratio, mg/mL), X_3 (time, min) and X_4 (temperature, °C), and the response was total phenolic content (TPC). Design-Expert 8.0.7.1 (trial version) software was used to apply the Box-Behnken Design Model. To have the most suitable set of variables, stepwise regression was used. According to this process, given variables are tested and assessed within the given alpha levels (0.1), using both backward and forward techniques. Backward technique includes all the variables to estimate parameters, and then any variables with a nonsignificant parameter at the given alpha levels are removed from the equation. This process continues until there are no significant variables left. Similar to backward technique, the forward technique also assesses the given variables within the given alpha levels. Aside from backward technique, the forward technique starts with no variables included in the equation. The significant variable with the highest value of standardized beta ($p<0.05$) is added to the equation. Then the next variable with the highest standardized beta value is assessed. If significant, the variable is added to the equation. This process continues until no significant variables are left. Two of these regressions gave the same results [30]. Twenty-nine experiments were conducted with five replications at the center values to evaluate the pure error sum of squares.

Experimental data were fitted to the quadratic model. The proposed quadratic model is shown as below in Eq. (1):

$$Y = \beta_0 + \sum_{i=1}^{4}\beta_i X_i + \sum_{i=1}^{4}\beta_{ii} X_i^2 + \sum_{i=1}^{4}\sum_{j=i+1}^{4}\beta_{ij} X_i X_j + e \quad (1)$$

where Y is the response, β_0 is the constant coefficient, X_i (i=1-4) is the non-coded variable, β_i is the linear, and β_{ii} is the quadratic, and β_{ij} (i and j=4) is the second-order interaction coefficients [31].

5. Prediction by Artificial Neural Networks

Feedforward neural network is one of the artificial neural networks applied to model experimental data. Neurons in the feedforward neural network are placed in the order of where any neuron only has connection with the next layer. Inputs fed through the neural network are processed first in the input layer, then intermediate layers, and lastly in the output layer. On the output layer the information fed to the neural network and processed in the layers is presented to the external world. Output from the ANN in feedforward neural network is not being used in the training process. Fig. 1 represents the mechanism of feedforward neural network. We used an ANN with four hidden layers to investigate the model with experimental data. It had four inputs and one output, consisting of 60 neurons in the input layer and two neurons in the output layer, respectively. 50, 60, 20 and 10 neurons were used in the hidden layers. Hyperbolic tangent function was used in the hidden layers as activation layer. The scaled-conjugate gradient was used as learning method. While the scaled-conjugate gradient method changes are adjusted in every step, the classical gradient method uses a constant learning coefficient, which is not always the shortest way of reaching the most appropriate values. To minimize the error in the process, changes are adjusted/investigated in the direction of conjugate gradient [32].

6. Statistical Analysis

Three replicate extractions were carried out for each of the samples followed by a minimum of three spectrophotometric measurements from each extract. The statistical software Design Expert (Trial version 8.0.7.1) was used to analyze the experimental data for an analysis of variance (ANOVA).

The relationship between the experimental data and the calcu-

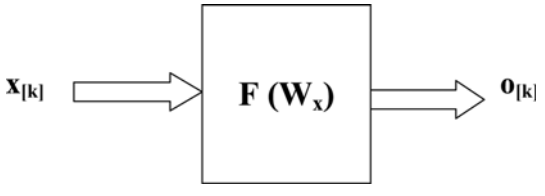

Fig. 1. Schematic of feedforward neural network.

lated quantities was evaluated through the correlation coefficient (R^2) and the root-mean-square deviations (rmsd) according to the following Eq. (2):

$$\text{rmsd} = \sqrt{\frac{\sum_{i=1}^{n}(C_{i,exp} - C_{i,cal})^2}{n}} \quad (2)$$

where n is the number of the experiments, $C_{i,exp}$ refers to the concentration value of experiment i, and $C_{i,cal}$ is the calculated concentration value of the i.

RESULTS AND DISCUSSION

1. Effect of Process Variables on the UAE Performance

Table 1 shows the design points consisting of four factors and their levels (lower, middle and upper). Experimental and predicted values acquired by both Box-Behnken design and artificial neural networks model are given in Table 2.

Table 1. Values of the independent variables and their coded forms with their symbols employed in RSM for optimization of olive leaves through UAE

Independent variables	Units	Symbols of the variables	Coded levels		
			−1	0	1
pH	pH	X_1	3	7	11
Solid/solvent ratio	mg/ml	X_2	500/10	500/15	500/20
Time	min	X_3	20	40	60
Temperature	ºC	X_4	30	45	60

Table 2. Box-Behnken design of the independent variables (X_1, X_2, X_3, X_4) and comparative results of experimental and predicted of TPC of olive leaf extracts using RSM and ANN approaches

Run order	X_1, pH	X_2, solid/solvent ratio (mg/mL)	X_3, time (min)	X_4, temperature (ºC)	TPC* (mg-GAE/g-DM)	Predicted TPC (ANN) (mg-GAE/g-DM)	Predicted TPC (RSM) (mg-GAE/g-DM)
29	3	500/10	40	45	31.13±0.04	31.13	33.63
2	11	500/10	40	45	22.16±0.10	22.16	20.39
9	3	500/20	40	45	36.06±0.33	36.06	39.09
22	11	500/20	40	45	25.72±0.38	25.72	25.85
11	7	500/15	20	30	38.83±0.11	38.83	35.56
20	7	500/15	60	30	32.21±0.13	32.21	32.87
21	7	500/15	20	60	35.40±0.16	35.40	33.15
27	7	500/15	60	60	47.58±0.24	47.58	49.27
18	3	500/15	40	30	36.61±0.40	36.61	37.43
1	11	500/15	40	30	24.28±0.13	24.28	24.19
28	3	500/15	40	60	46.21±0.15	46.21	44.42
12	11	500/15	40	60	29.56±0.13	29.56	31.18
23	7	500/10	20	45	26.54±0.14	26.54	27.06
19	7	500/20	20	45	29.6±0.16	29.06	32.52
16	7	500/10	60	45	35.06±0.15	35.06	33.78
15	7	500/20	60	45	42.16±0.23	42.16	39.24
25	3	500/15	20	45	33.30±0.04	33.30	31.08
10	11	500/15	20	45	21.56±0.15	21.56	21.68
8	3	500/15	60	45	43.98±0.11	43.98	41.64
4	11	500/15	60	45	24.55±0.23	24.55	24.56
3	7	500/10	40	30	31.37±0.09	33.21	31.48
24	7	500/20	40	30	35.17±0.19	37.90	36.95
17	7	500/10	40	60	35.66±0.04	35.61	38.47
14	7	500/20	40	60	46.00±0.12	44.81	43.94
5	7	500/15	40	45	32.96±0.06	30.66	33.15
7	7	500/15	40	45	32.83±0.08	30.66	33.15
26	7	500/15	40	45	32.78±0.09	30.66	33.15
6	7	500/15	40	45	32.95±0.07	30.66	33.15
13	7	500/15	40	45	32.90±0.08	30.66	33.15

*Data are expressed as the mean (n=9) ±S.D.

The results showed that the pH of the solvent systems had reverse effects on polyphenol content, as seen in Table 2. The TPC of the extracts had a tendency to decrease by increasing the pH of the solvent. This might be explained by the fact that an acidic media helps the cleavage of phenolics bonded to carbohydrate polymers and proteins. Our results are consistent with those of Wang et al. and Mylonaki et al. [33,34].

The TPC of the extracts increased by decreasing the ratio of solid to solvent. The increase of the yield by solvent content is consistent with mass transfer principles, since the driving force is supposed to be higher when a lower solid to solvent ratio is used. The TPC of the extracts increased steadily as a function of time. This might be explained by different time of equilibrium of each response variable. 60 min is accepted as the optimum time for the extraction of phenolics, whereas 40 min is enough time to give the equilibrium concentration of the extracted leaves.

Extractions of olive leaves were performed over temperatures ranging from 30 to 60 °C, since consuming much longer temperature is an impractical situation from the economical point of view. Expectedly, TPC of the extracts increased steadily as a function of temperature, since mass transfer and solute vapor pressure both increase by temperature.

2. Modelling of UAE using RSM

Using response surface methodology from the software, a quadratic model applied with not only forward stepwise but also backward elimination regression for TPC was derived. The equation is given below in Eq. (3):

$$Y=71.42715+2.28779X_1+0.54650X_2-0.36882X_3-2.21848X_4 -0.024031X_1X_3+0.015667X_3X_4-0.21300X_1^2+0.020276X_4^2 \quad (3)$$

When using response surface model, parameters were analyzed in detail. Binary interaction parameters were found as not only between pH and time but also between time and temperature. Furthermore, the linear terms of X_3 and X_4, the binary interaction of X_1X_3, and the quadratic term of X_1^2 have negative effect on the response, as seen in Eq. (3).

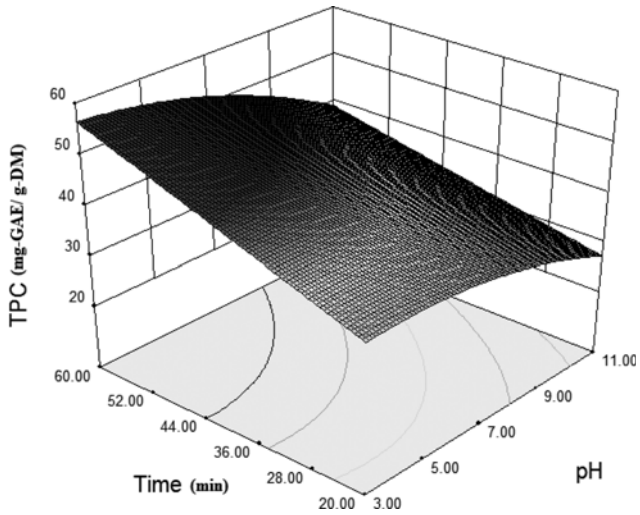

Fig. 2. Response surface plot for the TPC of the extracts as a function of extraction time to solvent pH (solid to solvent ratio =500 mg/19.78 mL; extraction temperature=59.87 °C).

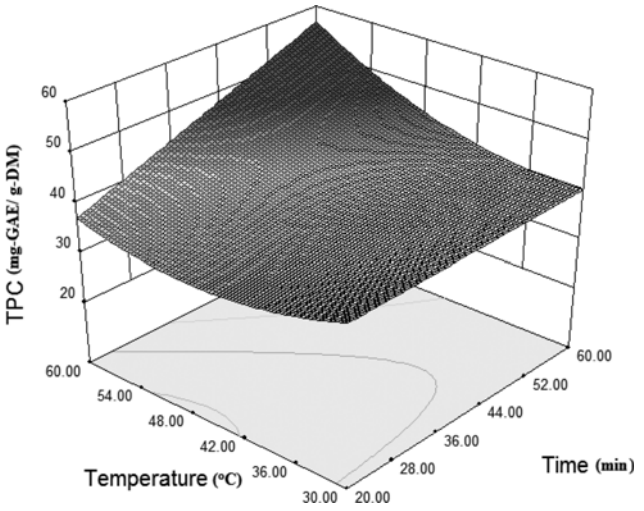

Fig. 3. Response surface plot for the TPC of the extracts as a function of extraction temperaure to extraction time (solid to solvent ratio=500 mg/19.78 mL; solvent pH=3.52).

The optimum experimental conditions were found by using optimization choice in Design Expert software to maximize the response. This value was measured at 3.52 of pH, 59.87 min, 59.87 °C and 500 mg/19.78 mL solid to solvent ratio. The maximum TPC was found as 56.17 mg-GAE/g-DM under those conditions.

The plots were constructed according to Eq. (3) for the TPC of olive leaves obtained by UAE as given in Fig. 2 and Fig. 3. Fig. 2 shows the effect of solvent pH and extraction time on the TPC of the olive leaf extracts at 59.87 °C and 500 mg solid/19.78 mL solvent. Increasing extraction time results in a higher TPC until a certain value of time. Generally, the response increases rapidly at the beginning of the process. After a while, the increase in response starts to slow down. The first step (rapid step), solvent penetrates the matrix, and mobilizes the solid. The second step (slower one) the desired extract diffuses from the matrix into the surrounding extraction solvent [35,36]. This process takes longer time and consumes much more energy. In addition to these disadvantageous, a longer extraction period might lead to degradation of antioxidant activities of polyphenols [37]. Thus, optimum time must be calculated from the predicted model. On the other hand, TPC is inversely proportional to pH. Lower pH values of solvent cause higher diffusion coefficients, leading to increases in cell membrane permability. This phenomenon was reported by Welti-Chanes et al., Tabart et al., Wang et al. 2007 and also by Ruenroengklin et al., in their studies [33,38-40].

Fig. 3 shows the effects of extraction time and temperature on the TPC of the olive leaves extracts at 3.52 of pH and 500 mg solid/19.78 mL solvent. Increasing both the temperature and time caused to increase the TPC of the extracts. This might be explained by the fact that diffusion coefficient is proportional to temperature [41]. This phenomenon was also reported by Juntachote et al. [42]. If the extraction temperature was kept constant, increasing extraction time resulted in a higher TPC until a certain value of time. The solute in the matrix and the extraction solution are in equilibrium with each other as explained by Fick's second law of diffusion [43].

The analysis of variance (ANOVA) for the quadratic equations

Table 3. The analysis of variance (ANOVA) for the quadratic equations of design expert 8.0.7.1 for the TPC

Source	Sum of squares	df	Mean square	F-value	P-value Prob>F
Model	1259.01	8	157.38	35.27	<0.0001
X_1-pH	526.16	1	526.16	117.86	<0.0001
X_2-Solid/solvent ratio	89.60	1	89.60	20.07	0.0002
X_3-Time	135.41	1	135.41	30.33	<0.0001
X_4-Temparature	146.58	1	146.58	32.83	<0.0001
X_1X_3	14.78	1	14.78	3.31	0.0838
X_3X_4	88.36	1	88.36	19.79	0.0002
X_1^2	80.16	1	80.16	17.96	0.0004
X_4^2	143.65	1	143.65	32.18	<0.0001
Residual	89.29	20	4.46		
Pure error	0.024	4	6.030E-003		
Cor total	1348.30	28			

of Design Expert 8.0.7.1 for the response of TPC is given in Table 3. Regression analysis was done at 95% of confidence interval. The obtained model F-value of 32.42 and $p<0.0001$ indicates that the derived model is significant. X_2, X_4, X_{22} are significant model terms between the confidence interval. All of the considered factors were found statistically significant with very low P-values ($p<0.0001$ and $p=0.0002$). The most significant of all was the pH of the media with the highest F-value (117.86). On the other hand, the interaction of pH and extraction time (X_1X_3) was found statistically insignificant with P-values higher than 0.05. In our study, the R^2 (0.9338) value for TPC displays good accuracy of the derived model. Thus, the response surface modelling can be achieved sufficiently to predict TPC from olive leaves with UAE. Also, the coefficient values of variation (C.V. %) are found as 6.28 for TPC. The lower coefficient of variation value indicates a higher precision and reliability of the experimental results [44,45].

Fig. 4 exhibits the correlation between the experimental and predicted data calculated from RSM model concerning the TPC in olive leaves obtained by UAE. It can be figured out that the predicted data calculated from the models are in good agreement with the experimental data according to the high correlation coefficient (R^2= 0.9315) and the low root mean squared deviation (rmsd=1.85).

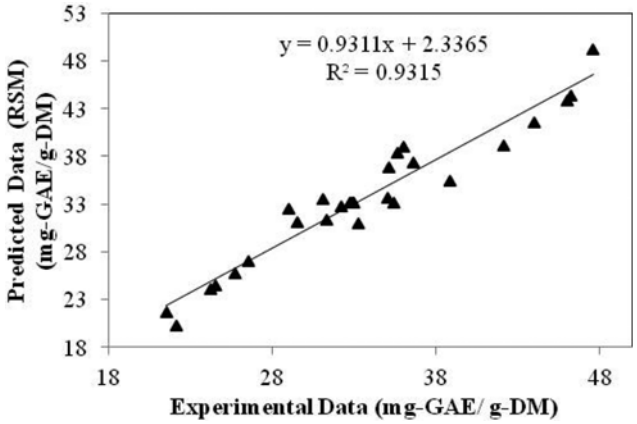

Fig. 4. The correlation between the experimentally obtained values of the TPC versus the calculated values using the model equation (RSM).

3. Modelling of UAE using ANN

The structure of the designed neural network model is represented in Fig. 5. The ANN structure used for the prediction of the present UAE process has the properties of four input neurons representing the independent variables (pH, solid/solvent, time and temperature), one output neuron representing the dependent variable (TPC). Twenty of the experimental data were used, and the remaining was used for testing. The training and test results are shown in Table 2.

The correlation between the experimentally obtained values and

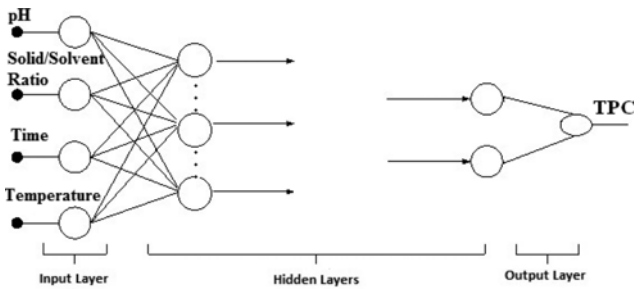

Fig. 5. Schematic of a multilayer feed-forward neural network consisting of four inputs, four hidden layers and one output.

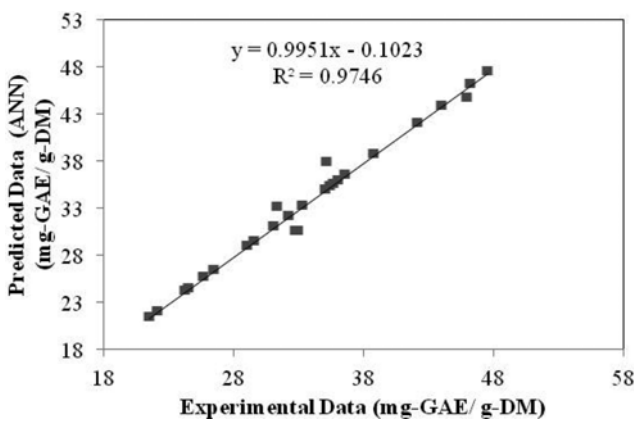

Fig. 6. The correlation between the experimentally obtained values of the TPC versus the calculated values using the model equation (ANN).

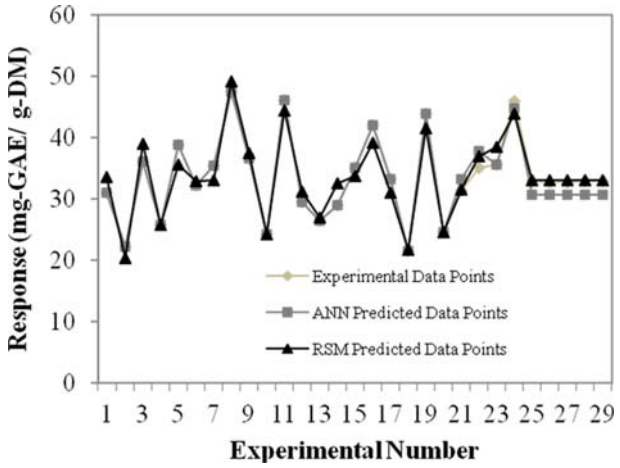

Fig. 7. Distribution of the responses obtained by experiments, RSM and ANN models.

the calculated responses for TPC in olive leaves is drawn in Fig. 6. The correlation coefficient of 0.9746 of the plot indicates the reliability of the ANN model in this system. On the other hand, the root mean squared deviation (rmsd=1.13) is low enough to show its high accuracy.

Fig. 7 shows the distribution of differences between the actual and calculated values of two approaches in order to compare them. The RSM model displays higher deviation than the ANN model.

CONCLUSIONS

Olive tree (*Olea europaea*) leaves were extracted by UAE, which is both an environmental and economical alternative to conventional extraction methods. The results of the RSM suggest that 3.52 of pH, 59.87 °C, 59.57 min and 500 mg dried matter to 19.78 mL solvent were predicted as the optimum parameters in terms of the maximum TPC (56.17 mg-GAE/g-DM). The linear, square and interaction coefficients of all the parameters were found statistically significant, except for the interaction of pH and extraction time. On the other hand, pH of the media was the most effective parameter of all. The RSM and ANN showed a good agreement with the experimental data, which allows its application in modelling and optimization of the UAE process for the extraction of high-added-value components from olive leaves. Finally, the present article is the first to investigate the ultrasound-assisted extraction of polyphenols from olive leaves, comparing the response surface methodology and artificial neural networks approaches on the process.

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