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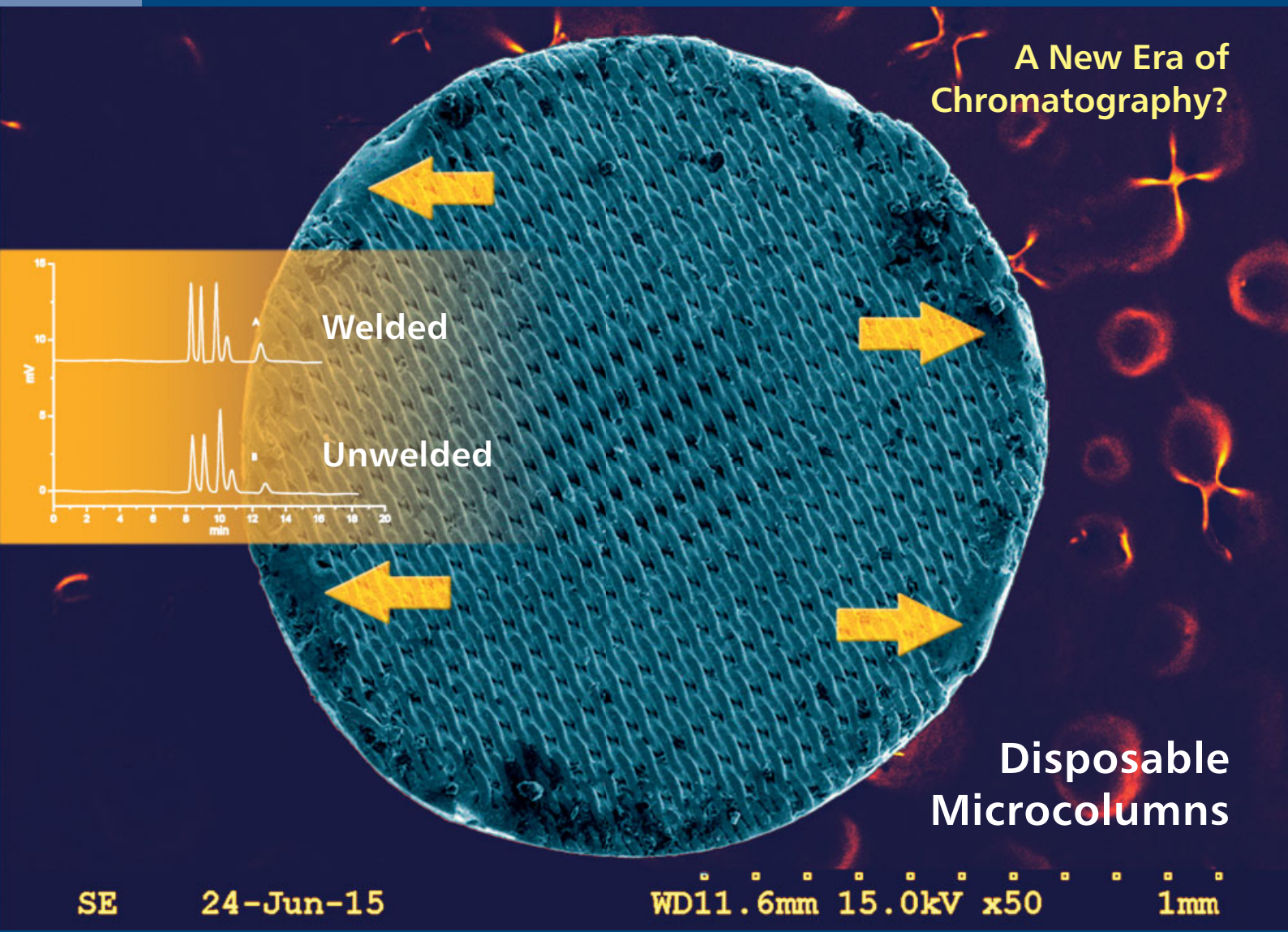

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Research Article

Monitoring the oleuropein content of olive leaves and fruits using ultrasound- and salt-assisted liquid–liquid extraction optimized by response surface methodology and high-performance liquid chromatography

A novel and rapid ultrasound- and salt-assisted liquid–liquid extraction coupled with high-performance liquid chromatography has been optimized by response surface methodology for the determination of oleuropein from olive leaves. Box–Behnken design was used for optimizing the main parameters including ultrasound time (*A*), pH (*B*), salt concentration (*C*), and volume of miscible organic solvent (*D*). In this technique, a mixture of plant sample and extraction solvent was subjected to ultrasound waves. After ultrasound-assisted extraction, phase separation was performed by the addition of salt to the liquid phase. The optimal conditions for the highest extraction yield of oleuropein were ultrasound time, 30 min; volume of organic solvent, 2.5 mL; salt concentration, 25% w/v; and sample pH, 4. Experimental data were fitted with a quadratic model. Analysis of variance results show that *BC* interaction, A^2, B^2, C^2, and D^2 are significant model terms. Unlike the conventional extraction methods for plant extracts, no evaporation and reconstitution operations were needed in the proposed technique.

Keywords: Liquid chromatography / Liquid–liquid extraction / Oleuropein / Olive / Salt-assisted extraction / Ultrasound
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1 Introduction

Sample preparation methods are used for enhancing the sensitivity and selectivity of analysis techniques [1–3]. The obtained sample in this step should have a high concentration of target analytes free of interfering compounds from the matrix. Therefore, the extraction of target analytes from a sample matrix is one of the most important steps in a sample preparation process.

Natural products extraction is usually performed with solid–liquid extraction (SLE) techniques including maceration, Soxhlet extraction (SE), supercritical fluid extraction (SFE), accelerated solvent extraction (ASE) and distillation [4–8]. The performance of the extraction technique depends on various parameters such as temperature, pressure, time, shaking, and extracting solvent nature. Although applying hard extraction conditions such as heat, pressure, and agitation usually lead to reduction in extraction time, their destructive effects on natural compounds must also be considered.

The conventional extraction of natural compounds using maceration, SE, and distillation techniques requires a large volume of organic solvent and longer extraction time. On the other hand, these techniques (SE and distillation) have destructive effects on natural compounds due to the high temperature of the process. In the conventional solvent extraction methods, due to the use of a large volume of extracting solvent and the incompatibility of most of these solvents with analytical instrument, evaporation to dryness and reconstitution of the extract in a very small volume of appropriate solvent are necessary [9–11]. Consequently, an increasing demand for the extraction of natural molecules by a clean and green extraction method with safe solvents at low temperatures is observed. The use of ultrasound-assisted extraction (UAE) and microwave-assisted extraction (MAE) methods for the extraction of natural compounds in comparison with conventional solvent extraction techniques have several advantages such as higher extraction efficiency, small solvent volume, and acceleration in extraction process [12–16]. However, preconcentration and cleanup of extract may be necessary before analysis.

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Abbreviations: ACN, acetonitrile; **ANOVA**, analysis of variance; **MAE**, microwave-assisted extraction; **RSM**, response surface methodology; **SALLE**, salt-assisted liquid–liquid extraction; **SE**, Soxhlet extraction; **SLE**, solid–liquid extraction; **THF**, tetrahydrofuran; **UAE**, ultrasound-assisted extraction; **USALLE**, ultrasound- and salt-assisted liquid–liquid extraction

Table 1. Independent variables and their coded and actual values used for optimization

Factor	Name	Units	Low actual	High actual	Low coded	High coded	Mean
A	Ultrasound time	min	10.0	50.0	−1.0	1.0	30.0
B	pH		1.0	7.0	−1.0	1.0	4.0
C	Salt concentration	% w/v	10.0	40.0	−1.0	1.0	25.0
D	Organic solvent volume	mL	1.0	4.0	−1.0	1.0	2.5

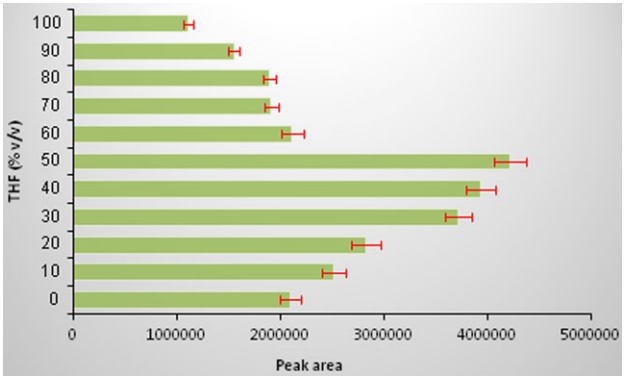

Figure 1. Effect of ACN/THF ratio on the extraction of oleuropein. Extraction conditions: aqueous phase pH, 3; organic phase volume, 3 mL; ultrasound time, 30 min; plant mass, 0.01 g; salt concentration, 10% w/v.

Salt-assisted liquid–liquid extraction (SALLE) is based on the phase separation of water-miscible organic solvents from the aqueous solution using the salt addition [17–19]. In this technique, water-miscible organic solvents with low toxicity were used as extracting solvents. Compared to liquid-liquid extraction (LLE), in the SALLE technique the large volume of toxic and immiscible organic solvent and vigorous mechanical shaking are not required. Also, in the SALLE evaporation of the extracting solvent and reconstitution the extract are not needed [20, 21]. There are several reports about the application of SALLE to determine the different compounds in various matrices [22–27]. Therefore, the coupling of SALLE with other extraction techniques such as UAE and MAE can lead to good results in terms of extraction efficiency, extraction time, preconcentration, and cleanup.

The aim of this work was to develop a novel ultrasound- and salt-assisted liquid–liquid extraction (USALLE) technique for the determination of oleuropein in olive leaves using response surface methodology (RSM). RSM is a collection of statistical and mathematical techniques that helps to develop and optimize the process with minimum experiments. In the proposed method, extraction, preconcentration, and cleanup are performed together. After UAE, extract was transferred to a microtube and exposed to the SALLE. Finally, upper organic phase was removed and injected into the high-performance liquid chromatography (HPLC) system. The influences of the main factors and their interactions on the extraction efficiency of oleuropein are illustrated using RSM.

2 Materials and methods

2.1 Chemicals

Oleuropein (purity ≥ 98% by HPLC) was purchased from Indofine Chemical Company (Hillsbrough, USA). Acetonitrile (ACN), tetrahydrofuran (THF), methanol, ethanol, sodium chloride, potassium dihydrogen phosphate, and orthophosphoric acid were purchased from Merck Chemical (Darmstadt, Germany). All solutions were prepared with deionized water from a Milli-Q system (Millipore, USA).

2.2 Samples

Olea europaea (variety: Sevillana) leaves and fruits were collected from Agricultural Research Garden, Khorramabad, Iran. Before the extraction, the leaves and fruits (after removing the stones) were dried, milled, homogenized, and kept at 4°C until analysis. The same sample was used in the whole optimization study.

2.3 Standard solutions preparation

A stock standard solution (1000 μg/mL) was prepared by dissolving oleuropein in methanol. Working standard solutions at concentration of 0.5–100 μg/mL were prepared by diluting the suitable volume of the stock standard with deionized water.

2.4 Chromatographic conditions

The HPLC system (Shimadzu Corporation, Kyoto, Japan) that consists of a quaternary pump (LC–10ATvp), UV-Vis detector (SPD-M10Avp), vacuum degasser, and system controller (SCL-10Avp) was used. A manual injector with a 10 μL sample loop was applied for loading the sample. Class VP-LC workstation was employed to acquire and process chromatographic data. A RP C_{18} analytical column (Shim-Pack VP-ODS, 250 × 4.6 mm id, Shimadzu Corporation) was used.

The mobile phase consisted of phosphate buffer (50 mM and pH 3 adjusted with orthophosphoric acid) and ACN (70:30, v/v). Before the preparation of the mobile phase, buffer solution and ACN were degassed separately using a Millipore vacuum pump. The UV detector was set at 254 nm. The

Table 2. Box–Behnken design with experimental conditions and responses for oleuropein extraction yield

Run	*A*: ultrasound time (min)	*B*: pH	*C*: salt concentration (% w/v)	*D*: organic solvent volume (mL)	Response: extraction yield (%)[a)]
1	50.00	7.00	25.00	2.50	0.7
2	30.00	1.00	10.00	2.50	2.5
3	30.00	4.00	25.00	2.50	13.3
4	30.00	4.00	40.00	4.00	3.1
5	30.00	4.00	25.00	2.50	12.85
6	30.00	7.00	40.00	2.50	4.45
7	50.00	4.00	40.00	2.50	3.1
8	30.00	7.00	25.00	1.00	0.8
9	50.00	4.00	25.00	4.00	0.11
10	10.00	4.00	40.00	2.50	1.35
11	30.00	7.00	10.00	2.50	1.15
12	30.00	1.00	25.00	4.00	0.55
13	30.00	4.00	25.00	2.50	13.4
14	10.00	4.00	10.00	2.50	2.45
15	30.00	4.00	10.00	1.00	1.1
16	30.00	4.00	25.00	2.50	13.45
17	10.00	7.00	25.00	2.50	0.205
18	30.00	1.00	40.00	2.50	0.42
19	50.00	4.00	25.00	1.00	0.5
20	10.00	4.00	25.00	1.00	0.2
21	30.00	1.00	25.00	1.00	1
22	10.00	1.00	25.00	2.50	0.2
23	10.00	4.00	25.00	4.00	0.5
24	30.00	7.00	25.00	4.00	1.05
25	50.00	4.00	10.00	2.50	2.75
26	30.00	4.00	40.00	1.00	0.75
27	30.00	4.00	25.00	2.50	12.4
28	50.00	1.00	25.00	2.50	0.49
29	30.00	4.00	10.00	4.00	2

a) Extraction yield (%) = (weight of the oleuropein in extract (g)) × 100/(weight of the plant sample(g)).

chromatograms were run for 10 min at a flow rate of 1.0 mL/min at ambient temperature.

2.5 Ultrasound and SALLE procedure

A total of 0.01 g of sample was transferred into a 15 mL conical polypropylene centrifuge tube. Ten milliliters of solvents mixture containing phosphate buffer (with variable pH), ACN, and THF in various percentages as extraction solvent were added to the tube and then the mixture was placed in an ultrasound bath at 25°C. After a certain time period, phase separation was completed by centrifuging the solution at 4000 rpm for 5 min and 1 mL of liquid phase was transferred into a microtube. Then NaCl salt was added to the microtube and mixture vortexes until dissolution of salt. Salt addition results in the rapid separation of two phases without centrifugation. Finally, 10 μL of organic phase was withdrawn and injected into the HPLC system for analysis.

2.6 Experimental design

Box–Behnken design was used to optimize the experimental conditions of the proposed method. According to preliminary experimental results, the ranges of independent parameters including ultrasound time, organic solvent volume, salt concentration, and pH were selected. The range and center point values of studied parameters are shown in Table 1. The extraction conditions were optimized using Design Expert 7.0 software package. Extraction yield of oleuropein was calculated according to the below equation.

$$\text{Extraction yield}\,(\%) = (\text{weight of the oleuropein in extract}\,(\text{g})) \times 100/(\text{weight of the plant sample}\,(\text{g})) \quad (1)$$

3 Results and discussion

3.1 Choice of organic solvent

To select an appropriate extracting solvent, two important parameters including the solubility of target compounds in extracting solvent and penetrability of extracting solvent into the sample matrix must be considered. Due to miscibility of extracting solvent in water, SALLE was applied for the extraction, preconcentration, and cleanup of polar

Table 3. ANOVA results for the proposed quadratic model

Source	Sum of squares	df	Mean square	*F* value	*p* value	Significant
Model	599.14	14	42.80	97.28	< 0.0001	Significant
A	0.63	1	0.63	1.43	0.2521	
B	0.85	1	0.85	1.93	0.1861	
C	0.12	1	0.12	0.28	0.6038	
D	0.73	1	0.73	1.66	0.2185	
AB	0.011	1	0.011	0.024	0.8794	
AC	0.53	1	0.53	1.19	0.2928	
AD	0.12	1	0.12	0.27	0.6111	
BC	7.24	1	7.24	16.45	0.0012	*
BD	0.12	1	0.12	0.28	0.6060	
CD	0.53	1	0.53	1.19	0.2928	
A^2	255.82	1	255.82	581.49	< 0.0001	*
B^2	246.13	1	246.13	559.48	< 0.0001	*
C^2	143.86	1	143.86	327.00	< 0.0001	*
D^2	265.01	1	265.01	602.39	< 0.0001	*
Residual	6.16	14	0.44			
Lack of fit	5.36	10	0.54	2.67	0.1784	Not significant
Pure error	0.80	4	0.20			
Cor total	605.30	28				
SD	0.66	*R*-squared		0.9898		
Mean	3.34	Adj *R*-squared		0.9796		
C.V.%	19.87	Pred *R*-squared		0.9470		
PRESS	32.11	Adeq precision		27.923		

*Significant ($p < 0.05$).

compounds from water or liquid samples. The choice of an appropriate organic solvent for maximum analyte extraction during SLE and SALLE steps is crucial. Several water-miscible organic solvents such as methanol, ethanol, ACN, THF, and their mixtures were examined as organic phase. No phase separation was observed using methanol, ethanol, and their mixtures with other solvents. The mixture of ACN/THF has shown higher extraction efficiency than pure ACN and THF. Thus, different ratios of ACN/THF were examined (Fig. 1). As can be seen from Fig. 1, the mixture of ACN/THF (50:50, v/v) shows the highest extraction efficiency for oleuropein. Therefore, the mixture of ACN/THF (50:50, v/v) was selected as organic solvent for experimental design.

3.2 Optimization of ultrasound and SALLE by RSM

After selection of organic solvent, to optimize the effect of other parameters, Box–Behnken design involving 29 runs was performed according to predicted conditions. To adjust of low and high levels of main variables, several preliminary experiments were performed. Table 2 shows the experimental design matrix and results for the proposed runs. The extraction yield of oleuropein ranged from 0.11 to 13.45%. The maximum yield was obtained for the 16th run under the experimental conditions of $A = 30$ min; $B = 4$; $C = 25\%$ w/v and $D = 2.5$ mL.

3.3 Extraction model and ANOVA analysis

Analysis of variance (ANOVA) results are shown in Table 3. The ANOVA results illustrate the value of the suggested model and determine the significant and nonsignificant model terms. If the *F*-test for lack of fit is significant, then the suggested model is not fitted with experimental data. Experimental data were fitted with a quadratic model by the following second-order polynomial equation:

$$\begin{aligned}\text{Extraction yield} = {} & +12.54 + 0.23A + 0.27B + 0.10C + 0.25D \\ & + 1.35BC - 6.01A^2 - 5.89B^2 - 4.44C^2 \\ & - 6.12D^2 \end{aligned} \quad (2)$$

Table 3 indicates that the R^2 (0.9898) and adjusted R^2 (0.9796) values for this model are satisfactory. Also, ANOVA results show that the *BC* interaction, A^2, B^2, C^2, and D^2 are significant model terms and the lack of fit was not significant at the 5% level ($p > 0.05$). These results indicate that the suggested model can satisfactorily explain the effects of ultrasound time, volume of organic solvent, salt concentration, and sample pH on the extraction yield of oleuropein using the USALLE method.

3.4 Optimization of the procedure

The effect of four parameters including ultrasound time (*A*), pH (*B*), concentration of salt (*C*), and volume of organic

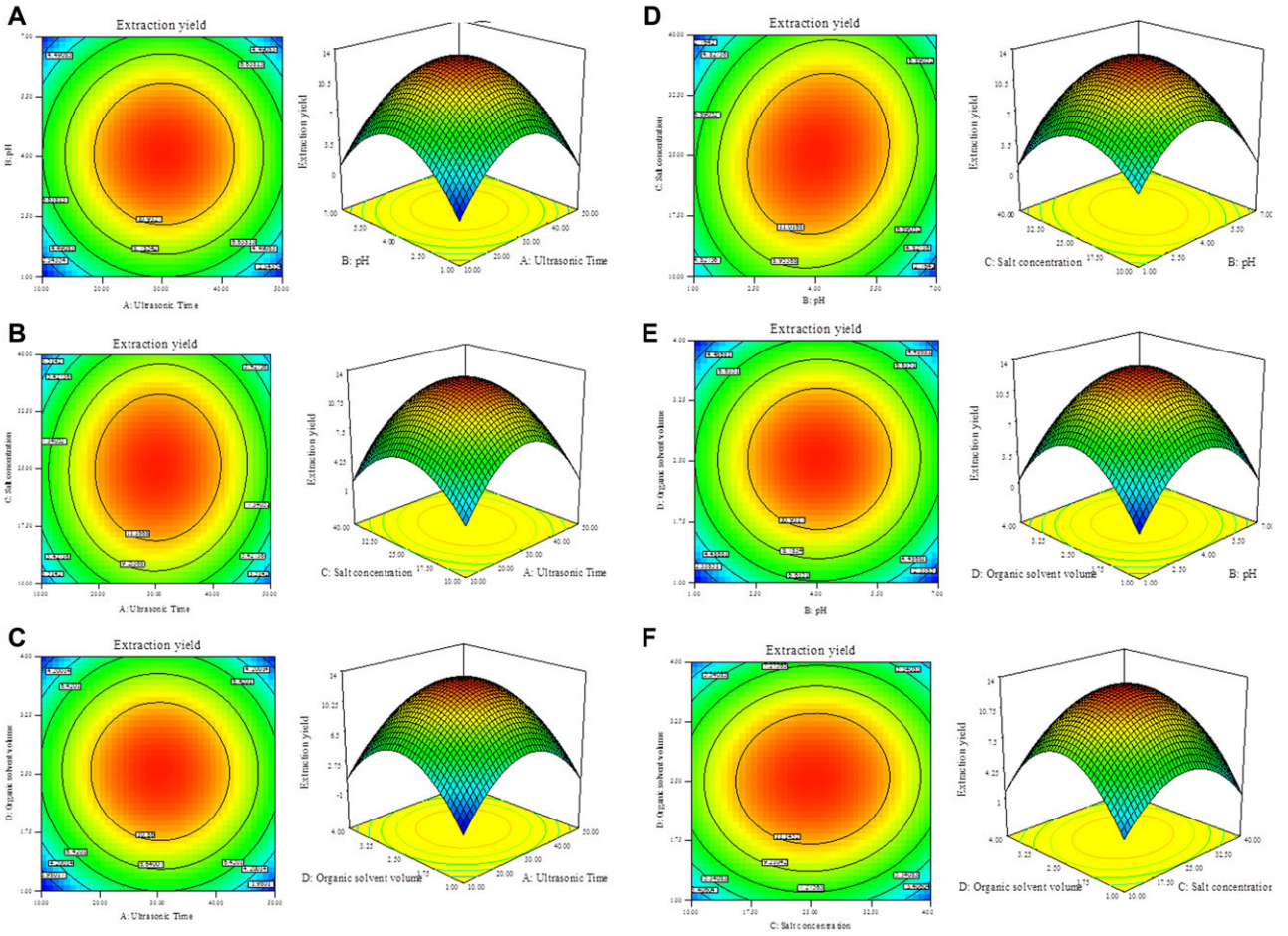

Figure 2. Response surface and contour plots for extraction yield of oleuropein as a function of ultrasound time (*A*), pH (*B*), concentration of salt (*C*), and volume of miscible organic solvent (*D*).

Table 4. The results of precision and accuracy tests under optimal conditions

Precision			Accuracy			
Conc. level (μg/ mL)	Intraday (RSD (%), $n = 3$)	Interday (RSD (%), $n = 9$)	Conc. added (μg/ mL)	Conc. found (μg/mL)	Recovery (%)	RSD (%), ($n = 3$)
5	5.2	7.5	5	4.6	92.0	6.5
10	5.5	6.7	10	9.0	90.0	5.2
50	4.8	5.4	50	48.5	97.0	4.0

Conc.; concentration.

solvent (*D*) on extraction yield of oleuropein is shown in 3D response surface and contour plots. The 3D plots reflect the effects of two variables on the response value, while the other variables were kept at zero level.

One of the main advantages of the ultrasound-assisted extraction is the shorter extraction time compared to conventional techniques. Figure 2A–C show the effect of ultrasound time on the extraction yield of oleuropein. The results indicated that the extraction efficiency increased with the increase of ultrasound time in the range of 10–30 min. After 30 min, the extraction efficiency was decreased. Increasing of ultrasound time can lead to degradation of oleuropein due to prolong exposure to ultrasound waves.

Since oleuropein is hydrolyzed at alkaline pH, the effect of pH on extraction was studied in the range of 1–7. As seen from Fig. 2A, D, and E, an increase in pH increases oleuropein extraction up to pH 4 and then decreases. This phenomenon is consistent with the p*I* (p*I* = 3.23) of the oleuropein. In the p*I*, net charge of oleuropein is zero that can increase mass transfer to organic phase.

Table 5. Comparison of several parameters for the USALLE, SE, and maceration methods

Parameter	Olive leaves			Olive fruits		
	USALLE	SE	Maceration	USALLE	SE	Maceration
Extraction yield of oleuropein (%; ±SD)	13.45 (±1.1)	2.2 (±0.98)	15.2 (±1.2)	0.24 (±0.98)	0.032 (±1.08)	0.28 (±1.02)
Sample weight (g)	0.01	5	5	0.01	5	5
Organic solvent volume (mL)	2.5	200	50	2.5	200	50
Extraction time (h)	30 min	16	24	30 min	16	24
Evaporation and reconstitution	—	Required	Required	—	Required	Required

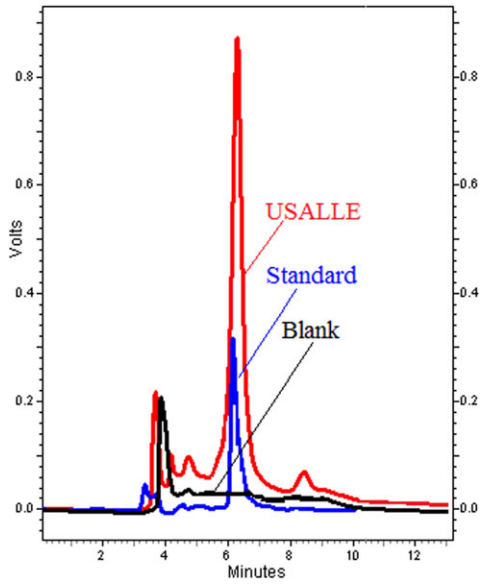

Figure 3. HPLC chromatograms of blank extract, direct injection of standard solution, and USALLME. Concentration of oleuropein in standard was 200 μg/mL. Extraction conditions: pH, 4; organic phase, ACN/THF (50:50 v/v); organic phase volume, 2.5 mL; ultrasound time, 30 min; plant mass, 0.01 g; salt concentration, 25% w/v.

The Organic solvent volume can influence the efficiency of the extraction. The Polarity of extraction solvent and volume of collected organic layer in SALLE step were varied with variation of organic solvent volume. Three different volumes of ACN/THF (50:50, v/v) including 1.0, 2.5, and 4.0 mL were investigated as organic solvent. As can be observed from Fig. 2C, E, and F, increase in the organic solvent volume up to 2.5 mL, first increases extraction yield and then decreases. In this method, analyte is completely extracted and then transferred to organic layer in SALLE step. On the other hand, low extraction efficiency at volumes less than 2.5 mL may be due to saturation of organic layer with analyte in SALLE step. Therefore, this behavior can be attributed to variation of extraction solvent polarity and organic solvent volume.

According to previous reports [28, 29] sodium chloride was selected as a suitable salt for the salting-out step. The effect of salt concentration in the range of 10–40% w/v was investigated. The results show that the extraction yield of oleuropein increased up to 25% w/v and then decreased (Fig. 2B, D, and F). Increasing the salt concentration can lead to an increase in analyte mass transfer from aqueous phase to organic phase. On the other hand, high salt concentration increases the viscosity of the aqueous phase, which reduces the mass transfer of analyte from aqueous to organic phase.

3.5 Model evaluation

Under the optimal conditions (ultrasound time, 30 min; volume of organic solvent, 2.5 mL; salt concentration, 25% w/v; and sample pH, 4), the maximum extraction yield of oleuropein (13.45%) was predicted by the proposed quadratic model. To investigate the reliability of the model a verification test was carried out under the optimal conditions. The result shows that the measured response (12.78%, $n = 3$) was in agreement with the predicted response. The obtained result demonstrates the performance of the quadratic model for the proposed USALLE–HPLC–UV method.

3.6 Method evaluation

Typical chromatograms of blank extract, standard solution, and extracted oleuropein under the optimized conditions are shown in Fig. 3. It is observed that USALLE is an effective method for extraction and preconcentration of oleuropein. Under the optimized conditions, validation parameters of the proposed method such as linearity, LOD, LOQ, precision, and accuracy were determined. The linearity of the USALLE–HPLC–UV method was evaluated by extracting and injecting standard solutions of oleuropein at different concentrations after extraction under the optimized conditions. The R^2 value of the calibration curve was 0.9984, which confirmed the linearity of the technique. The LOD and LOQ were 0.5 and 2.5 μg/mL, respectively.

Results of precision and accuracy tests of the proposed method in three concentration levels are detailed in Table 4. Intraday and interday RSD values for all concentration levels were less than 5.5 and 7.5%, respectively. Also, the obtained relative recoveries from the analysis of spiked samples were in the range of 90.0–97.0%.

To evaluate the application of the optimized USALLE technique, two samples (olive fruits and olive leaves) were

subjected to three extraction techniques including maceration, SE, and the proposed method. Maceration and SE were carried out according to our previous report [1]. The obtained results are listed in Table 5. The extraction yield of oleuropein using the proposed method was significantly higher than for the SE method. Unlike the maceration and SE methods, in the proposed method evaporation and reconstitution of extract were eliminated. Also, extraction time, sample amount, and volume of organic solvent in the USALLE method were reduced (Table 5). Due to LLE, the obtained extract using the USALLE was cleaner than maceration and SE methods.

4 Concluding remarks

In this study for the first time, USALLE as a new sample preparation method for solid samples was introduced and optimized using oleuropein as model analyte. The proposed method is based on coupling two extraction techniques including solid–liquid extraction and LLE techniques. Solid–liquid extraction and LLE were performed using UAE and SALLE, respectively. In this technique, high extraction efficiency of UAE for solid samples and preconcentration and cleanup features of SALLE were combined. Unlike the conventional extraction methods for plant extract no evaporative and reconstitute operations were needed in the USALLE technique. The organic phase can be directly injected to analytical instrument. Additionally, the centrifuging step was removed, and phase separation was facilitated by salt addition.

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The authors have declared no conflict of interest.

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