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Exploring Phenolic Diversity in *Quercus coccifera* L. Roots: HPLC-DAD Profiling and Mathematical Optimization through Response Surface Methodology

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Keywords

Quercus coccifera L., Root, HPLC-DAD, Phenolic, Optimization

ABSTRACT

The study aimed to investigate the effects and proportions of different extraction methods and phenolic compounds in extracts from the root of *Quercus coccifera* L. (QcRE). High-Performance Liquid Chromatography with Diode-Array Detection (HPLC-DAD) was used for mathematical modeling and optimization (MMO) using response surface methodology (RSM). The optimization aimed to maximize the phenolic compounds identified as Syringic acid (Sy-Ac), Gallic acid (GA), Fumaric acid (FA), Catechin (Ctc), Caffeic acid (Cf-Ac), 4-hydroxybenzoic acid (Hyb-Ac), and Catechin hydrate (Ctc-Hyd). The Design Expert program was used for RSM, with the conventional extraction time (30-120 min) as an independent variable. The best-predicted extraction parameter (Prd-90 min) was compared with microwave-assisted extraction (MAE) and accelerated solvent extraction (ASE). The optimal extraction time for conventional extraction was determined to be 90 min, with low deviation rates between real and predicted results (0.191% to 4.67%). The desirability value in the optimization was high at 0.973. In comparison, the highest yield was observed in Prd-90, followed by MAE and ASE. While the Sy-Ac results were similar across methods, GA was highest only in Prd-90. For other phenolic compounds, ASE showed the highest levels, decreasing for MAE and Prd-90. The study found that extraction times significantly affected phenolic compound components. The RSM model statistics indicated that only the Ex-Yld conformed to the criteria for a suitable model, with the cubic and quadratic models selected as optimal. The study highlighted the importance of extraction time in the optimization process, noting that prolonged exposure to heat could degrade phenolic compounds. The response surface plots showed 90 min as the optimal extraction time for most phenolic compounds, though some compounds had optimal durations of 52.5 min. The study concluded that extraction conditions significantly impact the yield and composition of phenolic compounds in QcRE.

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Introduction

There is a growing interest in evaluating and utilizing the antibacterial and antifungal properties of plants, not only for ethnobotanical studies but also for scientific research and various industrial applications. Plant roots and their secondary metabolites have long been employed in traditional medicine, as well as in the food, fragrance, and pharmaceutical industries for their beneficial properties (Alma, Karaogul, Ertas, Altuntas, Karaman, & Diraz, 2012; Hepsağ, Gölge, & Hayoğlu, 2016; Eyyup Karaogul & Alma, 2018; E. Karaogul, Kirecci, & Alma, 2016; E. Karaoğul, Altuntas, & Alma, 2017; EyyÜP KaraoĞUl, Hayoğlu, Cicek, Tascanov, Tanrıverdi, Cicek, et al., 2021; Koyuncu, Gönel, Temiz, Karaoğul, & Uyar, 2021; Nedjip & Karaogul, 2021; Ugurtay & Karaogul, 2022; Verep, Ates, & Karaogul, 2023; Yucegnul & Karaogul, 2021).

Evergreen oaks are the predominant species in many forest ecosystems across the Mediterranean region. Their dominance in these habitats significantly contributes to the region's biodiversity, ecological stability, and overall forest structure (Takhtajan, 1986). The Kermes oak (*Quercus coccifera* L.) holds significant ecological importance within the maquis vegetation of the Mediterranean region. Although its distribution overlaps with other oak species, distinct ecological differences are evident. *Quercus coccifera* is notably more thermophiles compared to other oak species, indicating its preference for warmer environments. It thrives predominantly in arid and disturbance-prone habitats, often found on limestone substrates. This species' adaptation to such specific environmental conditions underscores its role in maintaining the ecological balance and biodiversity of the Mediterranean maquis ecosystems (Martínez-Ferri, Manrique, Valladares, & Balaguer, 2004).

The rising global demand for non-wood forest products has underscored the necessity of sustaining these valuable resources. Ensuring their long-term availability requires the implementation of more effective and efficient utilization strategies. This involves adopting sustainable harvesting practices, enhancing the value chain, promoting the conservation of forest biodiversity, and fostering research and development to improve product yields and quality. By addressing these aspects, we can achieve a balance between meeting market demands and preserving forest ecosystems for future generations (Başyiğit, Sağlam, Hayoğlu, & Karaaslan, 2021; Hayoğlu & Toğrul, 2020; Komut, 2019; Yilmaz, Deniz, Fazli, Bekircan, Pranovich, & Karaoğul, 2024)

Forest lands provide not only wood raw materials but also a diverse array of non-wood products and derivatives. These include the by-products and wastes from wood raw materials, such as bark, roots, stems, shoots, leaves, and fruits of herbaceous plant parts. The utilization of these materials is essential for maximizing the economic and ecological value of forest resources. Research on the chemical composition of extracts from various parts of herbaceous and woody plants has revealed that these plants are rich sources of phenolic compounds. These compounds, known for their antioxidant, antibacterial, and antifungal properties, have significant potential for use in pharmaceuticals, nutraceuticals, and other industries. By exploring and harnessing the full spectrum of products obtainable from forest lands, we can promote sustainable forestry practices, enhance biodiversity conservation, and develop new economic opportunities based

on natural resources. (Verep, Ates, & Karaogul, 2023; Yusoff, Mat Taher, Rahmat, & Chua, 2022).

The aim of this work was to investigate bioactive component in the *Quercus coccifera* L. root by HPLC-DAD.

Materials and Methods

Roots of *Quercus coccifera* L. (QcRE) were harvested from Ahir Hill, located at an altitude of 1411 m in the Kahramanmaraş province of the Mediterranean region of Turkey. The geographical coordinates for the collection site were recorded as 37° 37' 15.11'' N latitude and 37° 03' 54.2'' E longitude. Taxonomic authentication of *Quercus coccifera* L. was conducted by Dr. Tolga OK from the Department of Forestry Engineering at Kahramanmaras Sutçu Imam University (KSU), Kahramanmaraş, Turkey. A voucher specimen (number 44) representing the collected plant material was deposited in the Herbarium of the Forestry Faculty at KSU (KASOF) for reference and future studies (E. Karaogul, Kirecci, & Alma, 2016).

Chemical standards, such as gallic acid, ellagic acid, caffeic acid, fumaric acid, catechin, protocatechuic acid ethyl ester, syringic acid, trans-3 hydroxycinnamic acid, 4-hydroxy benzoic acid, and (-)-gallocatechin, were procured from Sigma Chemicals Co. Solvents and reagents used in the study, including methanol, phosphoric acid, and acetonitrile, were of high-performance liquid chromatography (HPLC) grade and sourced from Merck Co. Throughout the experimental procedures, deionized water generated by a Millipore water purification system and filtered through a 0.22 µm membrane in the Central Laboratory of KSU was employed (E. Karaogul, Kirecci, & Alma, 2016).

Preparation of extracts

The roots of the Kermes oak were dried and pulverized by willey mill and sieved granulometric fraction for 40-60 mesh. The QcRE powders were used for extraction and HPLC analysis. About 2 g of QcRE powder was mixed with boiling water of 200 ml. The samples were extracted by using conventional hot water extraction method for 30, 60, 90 and 120 min, respectively. Half ml of each extract was removed and centrifuged at 5000 rpm for 10 min. The supernatant was collected and stored at 4 ^{o}C. Finally, extraction yields (Ex-Yld) were calculated as follows:

$$\text{Ex} - \text{Yld}\ (\%) = \frac{\text{Wo} - \text{W1}}{Wo} x100$$

where, Wo is the initial oven-dry weight of a sample before soaking in water (g) and W_1 is the oven-dry weight of the sample after extraction (g). The Accelerated Solvent Extraction (ASE) method is a system based on passing solvent through the sample within its own sample cup apparatus under pressure, with a temperature of 60°C. The total extraction process, including solvent boiling and filtration, was completed in 30 min. The microwave-assisted extraction unit operated by passing solvent through the sample within its designated sample cup apparatus under controlled conditions. The extraction was conducted at a temperature of 100°C for a duration of 20 min, utilizing the same amount and type of solvent as employed in CE.

The standard stock solutions of various phytochemicals were prepared following rigorous protocols. Gallic acid (200 mg/kg), caffeic acid (250 mg/kg), fumaric acid (300 mg/kg), catechin (200 mg/kg), syringic acid (120 mg/kg) and 4-hydroxybenzoic acid (400 mg/kg) were individually dissolved in methanol to achieve their respective concentrations. To maintain stability, these solutions were stored

under light-protected conditions at 4°C (E. Karaogul, Kirecci, & Alma, 2016).

Working solutions of desired concentrations were prepared by diluting the stock solutions appropriately. This meticulous preparation ensured the accuracy and reproducibility of the analytical methods employed in quantifying these phytochemicals from *Quercus coccifera* L. roots, facilitating precise characterization and assessment of their bioactive components in subsequent analyses.

HPLC-DAD

The HPLC analysis of oak root extracts was conducted using a DIONEX, HPLC system equipped with a diode array detector (DAD) detector. Phenolic compounds were detected at a wavelength of 278 nm. A ODS Hypersil C-18 column (250 x 4.6 mm x 5 µm) was employed for chromatographic separation. The elution was carried out using a mobile phase consisting of 0.1% phosphoric acid (A) and acetonitrile (B). The gradient elution profile was optimized as follows: starting with 8% B at 0 min, increasing to 22% B over 35 min, returning to 8% B at 45 min, and holding for 5 min to stabilize at initial conditions. The flow rate was maintained at 0.8 ml/min. Post-analysis, the chromatographic column was re-equilibrated with initial conditions for 10 min to ensure reproducibility.

To achieve optimal separation, various combinations of mobile phases including phosphoric acid-acetonitrile, acetic acid-methanol, methanol-acetonitrile, and methanol-water were investigated under different gradient conditions. The detection wavelength was based on the maximum absorption between 200nm and 400 nm wavelength for the reference compounds and samples. Identification of target components from *Quercus coccifera* L. roots was confirmed by comparing retention times. Following extensive validation, the column and the phosphoric acid-acetonitrile mobile phase were determined to be optimal for simultaneous separation and quantification.

Consistency between standard and sample spectra was observed across all analyzed samples, validating the reliability and accuracy of the HPLC method in quantifying phenolic compounds in the oak root extracts. These findings contribute to the comprehensive characterization of bioactive constituents in *Quercus coccifera* L., supporting further research in phytochemical analysis and pharmaceutical applications.

Table 1. Retention time, correlation coefficient of reference compounds on HPLC-DAD

No	Reference Compound	Retention Time (min)	Correlation coefficient % (R^2)
1.	4-hydroxybenzoic acid	14.42	98.3621
2.	Cafeic acid	20.51	99.0883
3.	Catechin hydrate	15.23	98.3892
4.	Catechin	14.93	99.8878
5.	Fumaric acid	4.78	99.1735
6.	Gallic acid	5.21	98.4451
7.	Syringic acid	23.53	99.9442

All calibration curves were constructed through linear regression analysis of integrated peak areas (x) versus concentrations (y, mg/kg) of the ten marker constituents present in the reference solutions across four distinct concentrations. The regression equations, retention times, and correlation coefficients for these ten marker constituents in the HPLC system are detailed in Table 1. This rigorous analytical approach ensures accurate quantification and validation of

the identified compounds in *Quercus coccifera* L. roots, facilitating comprehensive characterization and comparison with standard reference values. The data in this study were utilized from the Master's thesis titled "Extraction and HPLC Characterization of Some Oak Species (*Quercus*) Roots" conducted at the Institute of Science, Kahramanmaraş Sütçü İmam University.

Result and Discussion

Results

The objective of this study was to investigate the effects and proportions of extraction methods and phenolic compound components in extracts from the root of *Quercus coccifera* L. (QcRE) using High-Performance Liquid Chromatography with Diode-Array Detection (HPLC-DAD) for mathematical modeling (MMO) and optimization utilizing response surface methodology (RSM). Optimization studies were conducted to achieve maximum phenolic compound components. The design was created using the Design Expert program for RSM. For conventional extraction, the duration (30-120 min) was selected as an active function in the optimization as an independent variable.

Table 2. Experimental design and responses of extracts in root of *Quercus coccifera* L.

Indpendent	*Dependent*							
Extraction Type	Sy-Ac	GA	FA	Ctc	Cf-Ac	Hyb-Ac	Ctc-Hyd	Ex-Yld
CE-30	ND	11.431	ND	ND	ND	ND	ND	22.19
CE-60	11.218	8.145	3.639	ND	ND	0.727	ND	22.76
CE-90	12.604	19.074	0.848	2.773	5.379	ND	ND	23.16
CE-120	7.608	0.567	0.614	1.5	4.824	0.502	ND	22.82
Prd-90 min	12.580	19.110	0.810	2.8	5.430	ND	ND	23.09
U%	-0.192	0.191	-4.669	0.951	0.941	ND	ND	-0.303
MAE	13.298	13.362	3.845	7.527	9.648	ND	7.478	21.32
ASE	11.932	12.867	12.274	16.221	11.900	ND	16.117	18.09

Desirability: 0.973, Sy-Ac: Syringic acidi GA: Gallic acid, FA: Fumaric acid, Ctc: Catechin, Cf-Ac: Cafeic acid, Hyb-Ac: 4-hydroxybenzoic acid, Ctc-Hyd: Catechin hydrate, Ex-Yld: Extraction yield

The designs included independent and dependent variables, which were presented in Table 2. The phenolic compounds were identified as Syringic acid (Sy-Ac), Gallic acid (GA), Fumaric acid (FA), Catechin (Ctc), Caffeic acid (Cf-Ac), 4-hydroxybenzoic acid (Hyb-Ac), and Catechin hydrate (Ctc-Hyd) based on references through HPLC-DAD. Additionally, extraction yield (Ex-Yld) was used in the optimization. After optimization with RSM and MMO, the best-predicted extraction parameter (Prd-90 min) was compared with microwave-assisted extraction (MAE) and accelerated solvent extraction (ASE). In CE, the optimal extraction time was determined to be 90 min, and the predicted results for the dependent variables were derived. The deviation rates (U%) between experimental and predicted results ranged from 0.191% to 4.67%, indicating a very low deviation rate (Table 2). These predicted values were compared with MAE and ASE (Figure 1). The desirability value in the optimization was at a high acceptable level of 0.973. In a similar study, Karaogul et al. analyzed the phenolic compound components of QcRE using HPLC-UV detector. (E. Karaogul, Kirecci, & Alma, 2016). In the comparison of methods, the

highest yield was observed in Prd-90 and subsequently in MAE and ASE. For Sy-Ac, the results across all methods were nearly similar. However, GA was at the highest level only in the Prd-90 method..

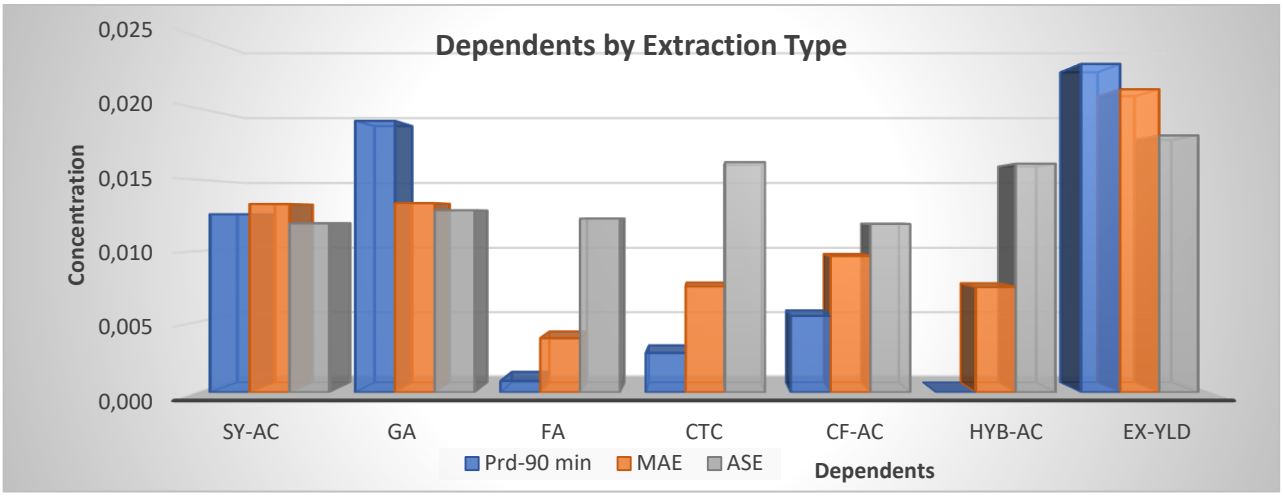


Figure 1. Phenolic compound levels in root of *Quercus coccifera* L. extracted by predicted CE, MAE and ASE

Table 3. Model equation statistics of the dependents on responses surface methodology of extracts in root of *Quercus coccifera* L.

Response	Coefficient Type	Std. Dev.	R_{prd}^2	R^2_{adj}	F Value	p-Value	Lack of fit	Remarks
Sy-Ac	Linear	4.461	0.306	0.237	4.419	0.0619	< 0.0001	
	Quadratic	0.445	0.994	0.992	994.249	< 0.0001	< 0.0001	
	cubic	0.005	1.000	1.000	66825.4	< 0.0001	< 0.0001	suggested
GA	Linear	6.781	0.133	0.046	1.531	0.2442	< 0.0001	
	Quadratic	5.638	0.461	0.341	5.467	0.0441	< 0.0001	
	cubic	0.184	0.999	0.999	8425.4	< 0.0001	< 0.0002	Suggested
FA	Linear	0.006	-0.094	-0.363	0.058	0.8148	< 0.0001	
	Quadratic	0.484	0.370	0.194	8.355	0.0179	< 0.0001	
	cubic	1.000	1.000	1.000	49481.1	< 0.0001	< 0.0001	suggested
Ctc	Linear	0,905	0.492	0.441	9.680	0.0110	< 0.0001	
	Quadratic	0.881	0.567	0.471	1.569	0.2419	< 0.0001	
	cubic	0.002	1.000	1.000	2228895	< 0.0001	< 0.0001	Suggested
Cf-Ac	Linear	1.394	0.753	0.728	30.410	0.0003	< 0.0001	
	Quadratic	1.461	0.755	0.701	0.108	0.7497	< 0.0001	
	cubic	0.033	1.000	1.000	17697	< 0.0001	< 0.0001	Suggested
Hyb-Ac	Linear	0.334	0.075	-0.017	0.815	0.3880	< 0.0001	
	Quadratic	0.346	0.107	-0.092	0.316	0.5877	< 0.0001	
	cubic	0.007	1.000	1.000	20625	< 0.0001	< 0.0001	Suggested
Ex-Yld	Linear	0.312	0.517	0.469	0.0006	10.725	0.0084	
	Quadratic	0.143	0.909	0.889	0.2382	38.689	0.0002	Suggested
	cubic	0.138	0.924	0.896		1.625	0.2382	

Desirability: 0.973, Sy-Ac: Syringic acidi GA: Gallic acid, FA: Fumaric acid, Ctc: Catechin, Cf-Ac: Cafeic acid, Hyb-Ac: 4-hydroxybenzoic acid, Ctc-Hyd: Catechin hydrate, Ex-Yld: Extraction yield

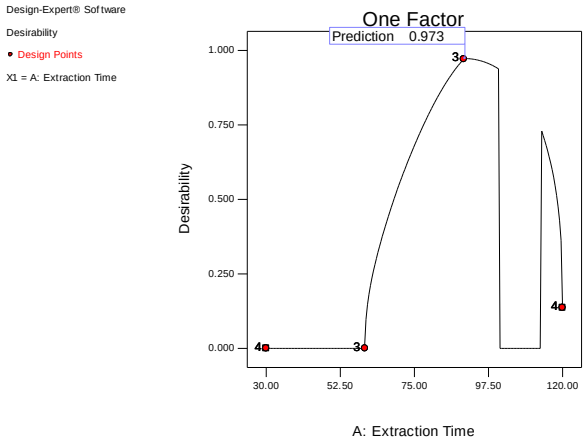
Table 4. Model coefficients and analysis of variance (ANOVA) and mathematical modelling outputs belonging to root of *Quercus coccifera* L.

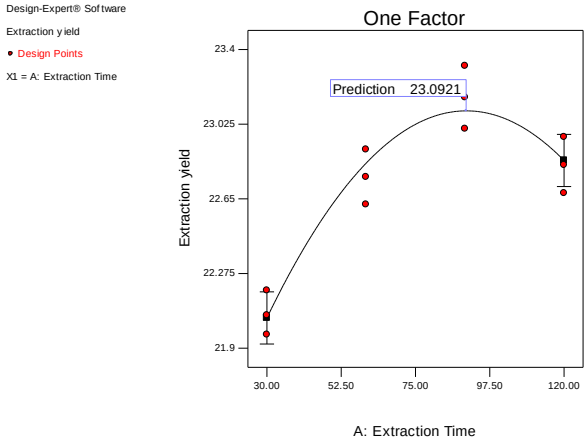
Coefficient Value		*Sy-Ac*	*GA*	*FA*	*Ctc*	*Cf-Ac*	*Hyb-Ac*	*Ex-Yld*
	Ω0	-24.49*	72.577*	-19.06*	9.594*	16.69*	-4.862*	20.76*
Linear	*Ω1 (Ex-Tm)*	1.076*	-3.488*	0.992*	-0.555*	-0.960*	0.261*	0.052**
Interaction	*Ω11 (Ex-Tm × Ex-Tm)*	-0.009*	0.056*	-0.014*	0.009*	0.016*	-0.004*	0.000
Second Order	*Ω111 (Ex-Tm × Ex-Tm × Ex-Tm)*	2.13E-05*	-2.70E-04*	5.55E-05*	-4.20E-05*	-6.98E-05*	1.66E-05*	0
Selected Models		Cb	Cb	Cb	Cb	Cb	Cb	Qd
Model: Y (response, ppb) = Ω0 + Ω1 (Ex-Tm) + Ω11 (Ex-Tm × Ex-Tm) + Ω111 (Ex-Tm × Ex-Tm × Ex-Tm)								

Ex-Tm: Extraction-Time , Cb: Cubic, Qd: Quadratic, Sy-Ac: Syringic acidi GA: Gallic acid, FA: Fumaric acid, Ctc: Catechin, Cf-Ac: Cafeic acid, Hyb-Ac: 4-hydroxybenzoic acid, Ctc-Hyd: Catechin hydrate, Ex-Yld: Extraction yield, Statistical significance levels: *P<.0001, **P<.001,

In contrast, GA, FA, Ctc, Cf-Ac, Hyb-Ac, and Ctc-Hyd were at the highest levels in ASE, and the amounts decreased sequentially for MAE and Prd-90. Optimization determined that extraction time significantly affected the phenolic compound components. This finding was also consistent with the literature (Hamad, Alma, Gulcin, Yilmaz, & Karaogul, 2017; E. Karaogul, Kirecci, & Alma, 2016)

The RSM model statistics were provided in Table 3. In the model statistics for RSM, the appropriate coefficient equation model (CEM) for the response was determined based on several criteria. These criteria included the values of R_{exp}^2 (~1), R_{adj}^2 (~1), Lack of Fit (LoF) with P > 0.05, and the F value with P<0.05. The selection process aimed to ensure that the model accurately represented the data while minimizing any lack of fit, thereby validating the robustness and reliability of the chosen model (Eyyup Karaogul & Nedjip, 2024; Yıldırım, 2021, 2022; Yıldırım, Bayram, & Öner, 2014; Yildirim, Öner, & Bayram, 2011; Yildirm, 2017). The evaluated CEMs included Linear, 2FI, Quadratic, and Cubic models. Among these, only Ex-Yld conformed to the criteria.





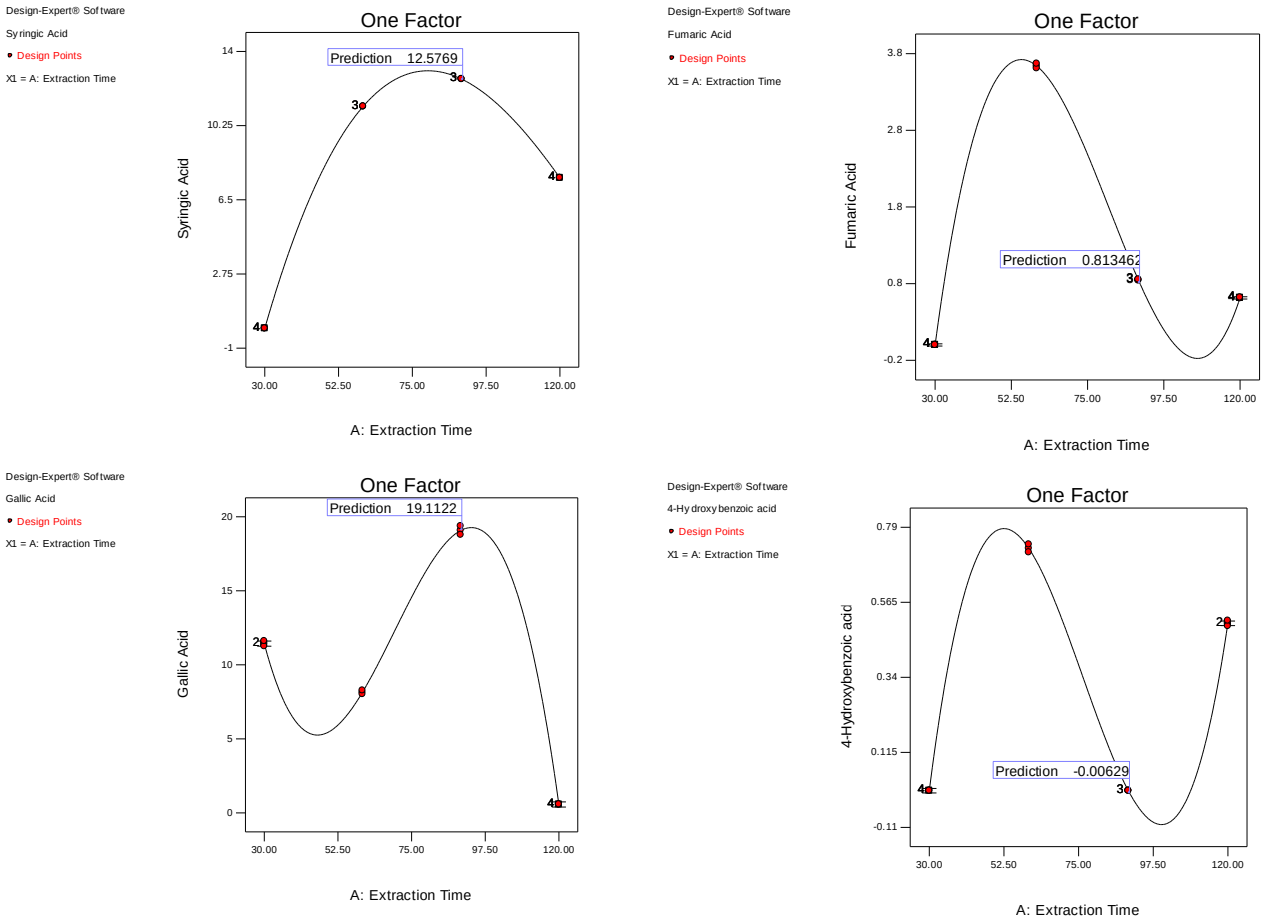
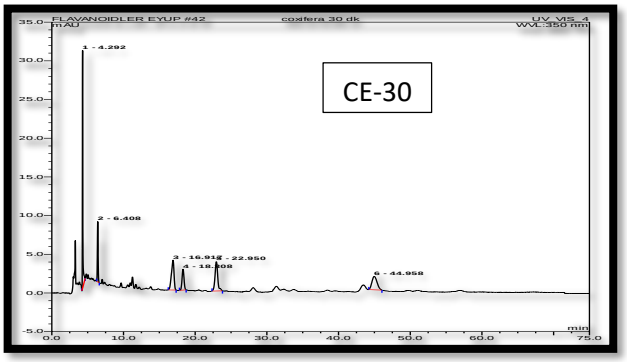


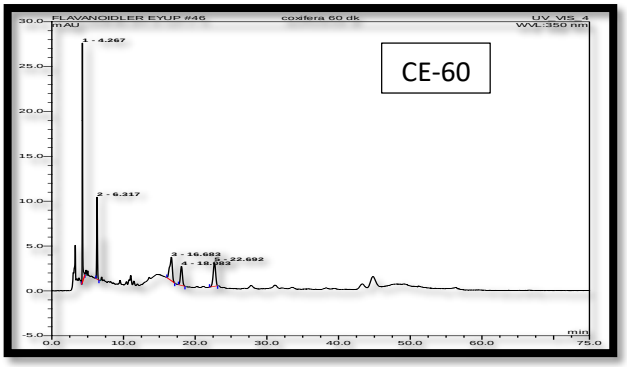
Figure 2. Response surface plots of outputs belonging to root of *Quercus coccifera* L.

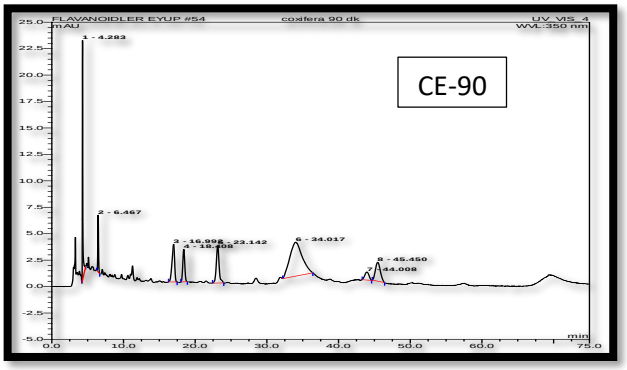
The optimal models that could be selected within the acceptable ranges were Cubic and Quadratic models. The others showed significance levels of $P < 0.0001$. However, the LoF values were not $P > 0.05$. The specified significance levels indicated high precision for the HPLC-DAD used in the study and demonstrated that deviation was not present under all conditions. This implies that the model did not adequately represent the data, indicating a significant lack of fit. In such cases, the model may not sufficiently capture the data patterns, necessitating a more complex model.

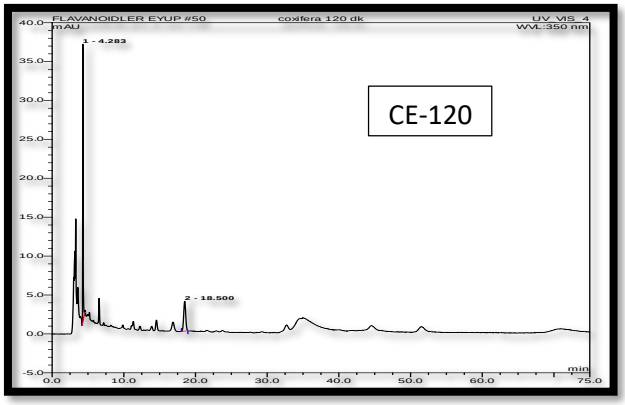
Thus, if the extraction type or time had been inadequate in extracting phenolic component components under all conditions, the LoF value would have been higher. This suggests that these

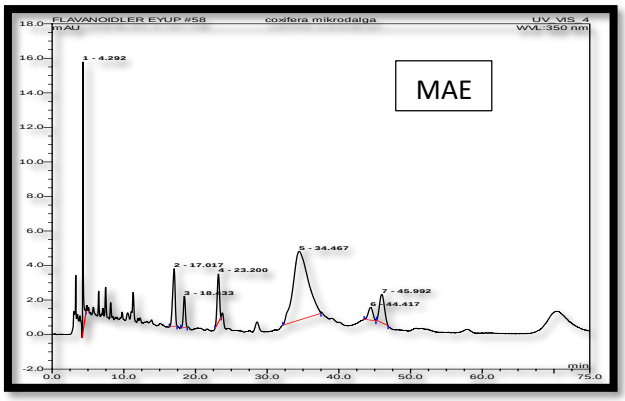
phenolic compounds are present in such high concentrations in QcRE that every condition was sufficient for their extraction (Table 3). Table 4 presents the model coefficients, analysis of variance (ANOVA), and mathematical modeling outputs related to QcRE. The mathematical equations, coefficients, and selected models based on the extraction method are shown in the Table. The significance levels of the independent variables against the responses are indicated by the "*" icon, which is defined at the bottom of the table. Nearly all the dependent variables had a significance level of P<0.0001 for Ex-Tm.











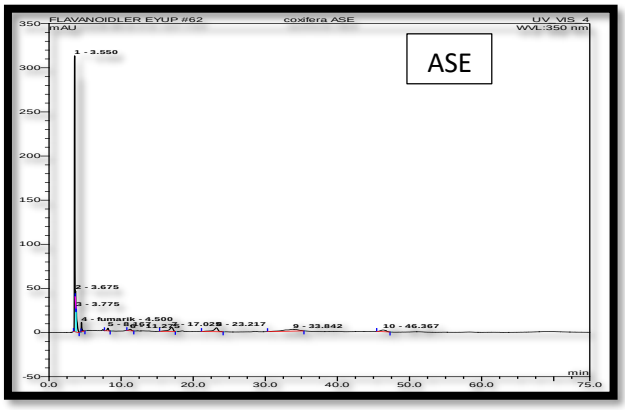


Figure 3. Chromatograms of extracts in root of *Quercus coccifera* L.

Figure 2 displayed the response surface plots of the outputs related to QcRE. Although optimization determined 90 min as the most optimal extraction time, this varied for different phenolic compounds. The acceptable time for Ex-Yld, Sy-Ac, GA, Ctc, and Cf-Ac was indeed 90 min. However, for the target phenolic compounds Hyb-Ac and Ctc-Hyd FA, the optimal time was observed to be 52.5 min. This indicated

that prolonged exposure to heat degraded phenolic compound components and caused their transformation within the extract (Figure 2). Additionally, Figure 3 depicted the chromatograms of the respective extracts.

Conculusions

Based on the findings and analyses presented in this study, several conclusions were drawn regarding the extraction methods and phenolic compound components in *Quercus coccifera* L. root extracts (QcRE):

Optimal Extraction Parameters: The study optimized extraction time using response surface methodology (RSM) and determined that 90 min was generally optimal for maximizing extraction yields (Ex-Yld) of phenolic compounds such as Syringic acid (Sy-Ac), Gallic acid (GA), Catechin (Ctc), and Caffeic acid (Cf-Ac). However, specific phenolic compounds like 4-hydroxybenzoic acid (Hyb-Ac) and Catechin hydrate (Ctc-Hyd) showed optimal yields at a shorter duration of 52.5 min. This variability suggested differential heat sensitivity and transformation rates of these compounds during extraction.

Comparative Analysis of Methods: Comparison with microwave-assisted extraction (MAE) and accelerated solvent extraction (ASE) indicated that while 90 min (Prd-90) generally yielded high results, ASE often surpassed in extracting higher quantities of GA, FA, Ctc, Cf-Ac, Hyb-Ac, and Ctc-Hyd. This underscored the influence of extraction method on specific phenolic compound yields.

Model Validation: The RSM model utilized in this study demonstrated robustness for predicting extraction yields, evidenced by high R_{exp}^2 and R_{adj}^2 values close to 1, indicating good fit to the data. The selection of appropriate coefficient equation models (CEMs) such as Cubic and Quadratic further supported the model's accuracy in representing the complex relationships between extraction variables and phenolic compound outputs.

Implications for Research and Application: The study's findings aligned with existing literature, highlighting the significant impact of extraction time and method on phenolic compound extraction from QcRE. The high concentrations of these compounds in QcRE suggested that varying extraction conditions could sufficiently extract these valuable bioactive compounds under different circumstances.

In conclusion, this research contributed valuable insights into optimizing extraction protocols for maximizing phenolic compound yields from *Quercus coccifera* L. roots, thereby informing future studies and applications in pharmaceuticals, nutraceuticals, and other related fields.

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