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Response Surface Methodology for Optimizing Parameters of the Ultrasound-Assisted Extraction of Total Phenolic Content of *Oxalis corniculata* Leaves

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Abstract: *Oxalis corniculata* Linn. Oxalidaceae) is one of the significant medicinal plants to treat liver diseases, jaundice, and urinary tract disorders and skin diseases in traditional medicine. The aim of this study was to use ultrasound assisted extraction method for extracting polyphenolic compounds from *O. corniculata* leaves, and also to optimize the various extraction parameters, i.e. solvent concentration, time of extraction and operating temperature. The central composite rotatable design (three factor-five level) was used to develop response surface methodology (RSM) model and to optimize the best extraction conditions of *O. corniculata* leaves. The analysis revealed that all the independent variables were significant ($p < 0.05$) to the responses which implied that the extraction parameters used in this study were vital in the optimisation process. The R^2 values of the response, i.e. total phenolic content (TPC) was 0.9965 which indicated that the quadratic polynomial models, developed were satisfactorily accurate to be used in the analysis of the interactions of the parameters (response and the independent variables). The optimum conditions found in RSM could be applied in future upscale extraction of the leaves of *O. corniculata* taking into consideration the temperature, extraction time and solvent for the economical analysis.

Keywords: *Oxalis corniculata, Total Phenolic Content, Optimization, Ultrasound Assisted Extraction, Response Surface Methodology.*

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I. INTRODUCTION

Public discontent regarding synthetic additives led to growing demand for natural extracts that began appearing in significant numbers during the past several decades. The antioxidants along with essential oils, proteins, fats, dietary fibres, dyes and saponins are different types of primary and secondary metabolites within natural extracts sourced from multiple plant materials [1-3]. Representative methods of extraction used by researchers on medicinal plants are maceration, decoction, infusion, digestion, percolation and Soxhlet extraction or, alternatively, ultrasound-assisted, superficial extraction and microwave-assisted extraction processes when working with medicinal plants [1,2]. Recently, ultrasound-assisted extraction (UAE) was reported to have many advantages and benefits over the other advanced extractions technologies [4]. UAE shows distinct advantages through its shortened extraction period because the method helps in preserving the compounds from degradation while protecting them against hydrolysis and oxidation [5].

Polyphenolic compounds are one of the key class of compounds that act mainly as antioxidants which add medicinal value to many plants [6]. Several authors studied phenolic compounds extraction from the natural sources by UAE method and suggested that three main parameters, which have a significant impact on the extract composition, are the concentration of the solvent, the time of ultrasound and the temperature of ultrasound [7-13]. The extraction of polyphenolics in plants and plant foods by the use of polar solvents methanol and ethanol has been employed over the past few years [14]. It has been noted that ethanol has been the first preference since it is less toxic as compared to methanol and other organic solvents and it has the greatest affinity to phenolic compounds [15].

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One of the important medicinal plants is *Oxalis corniculata* Linn. which has many pharmacological activities and is originating from the tropics and subtropics [16,17]. The Phytochemicals from *O. corniculata* exist in several chemical classes including flavonoids, tannins, phytosterols, phenols, glycosides, fatty acids and galactoglycerolipids and essential oils and important minerals [17,18]. Various investigations demonstrate the bioactive compounds extraction from *Oxalis corniculata* by different traditional methods yet minimal research exists on the extraction of polyphenolics from *O. corniculata* by novel emerging techniques.

In order to improve the analysis procedures, medicine sectors employ response surface methodology (RSM) widely [19-22]. RSM consumes lesser time and relatively not much labor intensive in implementing as compared to other strategies since a lesser number of the experimental trials are required to analyze a myriad of parameters and their interactions. The two most frequently utilised types of the RSM that have been employed in most experiments include central composite rotatable design (CCRD) and box-Behnken design (BBD). The BBD requires the minimum number of levels i.e. three levels of each factor to be able to fit a second-order regression model as compared to CCRD with five levels of each factor. Further, fewer experiment runs are often required in the BBD. Nevertheless, CCRD shows a lower Residual Standard Error (RSE) value than that of BBD in all the variables, indicating that CCRD can predict more accurate information than what is observed in the actual experiment. This denotes that CCRD is a better and improved design than BBD [23]. Therefore, the proposed research is aimed to optimize the extraction conditions of the UAE (ethanol concentration, ultrasonic temperature and ultrasonic time) to determine the total phenolic content (TPC) of *Oxalis corniculata* leaves.

II. MATERIALS AND METHODS

➢ *Materials*

Gallic acid, Folin–Ciocalteu's phenol reagent and sodium carbonate were purchased from Sigma-Aldrich (India). All other reagents were obtained from Merck, India and of analytical grade. Purified distilled water was prepared in the laboratory. The device used for the ultrasonic extraction was an ultrasonic bath, Bransonic 2200.

➢ *Sample Preparation*

Oxalis corniculata leaves were collected from Baddi, Himachal Pradesh, India. These leaves were then air dried in the shade at 28-30ºC. The sample was milled using a grinder with up to 500 µm mesh. The dried material was stored in a dry and cool place at 4ºC until analysis to avoid any chemical decomposition and reduced to smaller particles before extraction.

➢ *Phytochemical Analysis*

UAE of powdered plant material of *O. corniculata* Linn in different solvents like ethanol, ethyl acetate and petroleum ether was performed. These three *O. corniculata* extracts were then subjected to qualitative analysis to identify the kind of chemical constituents present in the extracts. The presence of carbohydrates, flavonoids, alkaloids, glycosides, saponins, tannins/phenolic compounds and terpenoids in the extracts were confirmed by the phytochemical screening using the standard method.

➢ *Total Phenolic Content (TPC)*

The Folin Ciocalteu is a measure of total concentration of the phenolic hydroxyl groups. Folin Ciocalteu reagent combines with polyphenols contained in the plant extract forming blue-colored complex compounds that can be measured quantitatively using a visible light spectroscopy method. The absorption of this blue complex takes place in the alkaline solution [24]. The total phenolic content in the extracts was determined using Folin Ciocalteu reagent and with Gallic acid as a standard. The total phenolic concentration was measured in mg/g of the extract.

➢ *Optimization of UAE by Single-Factor Experiments*

- *Effect of Extraction Temperature:*

Different extraction temperatures (20, 30, 40, 50, 60, 70 and 80 ºC) were used to select the best extraction temperature.

- *Effect of Extraction Time:*

Different extraction times (10, 20, 30, 40, 50, 60 and 70 min) were studied to select the optimum time, using the conditions as extraction temperature of 60ºC, 60% ethanol concentration and liquid/solid ratio as 30 mL/g.

- *Effect of Solvent Concentration:*

To study the influence of ethanol concentration on TPC, 5.0 g of powdered samples were put in 250 mL glass conical flasks and ethanol (varying from 30–90%, v/v) was added to these flasks. The temperature, time and the liquid/solid ratio for extraction was set at 60ºC, 60 min. and 30 mL/g, respectively.

➢ *Experimental Design for the Response Surface Procedure*

A central composite rotatable design (three-factor-five level) was employed to construct response surface methodology (RSM) model and to measure the optimum extraction conditions of *O. corniculata* leaves. In this study, the independent variables chosen toward the response TPC (mg/g) were extraction time (min), extraction temperature (°C) and solvent ratio (ethanol:water). Design Expert ® software (Version 7, Stat. Ease Inc., Minneapolis, USA) was used to generate a total of 19 experiments with three independent variables.

- *Statistical analysis:*

A predictive mathematical equation (eq. 1) that determined the interactions and variables' effects on the response was obtained by subjecting the gathered data to quadratic polynomial modelling [25].

$$Y = \beta_0 + \sum_{i=1}^{3} \beta_i x_i + \sum_{i=1}^{3} \beta_{ii} x_i^2 + \sum_{i=1}^{2} \sum_{j=i+1}^{3} \beta_{ij} x_i x_j \quad \text{..... eq. (1)}$$

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Where,

β_0, β_i, β_{ii}, and β_{ij} denotes the regression coefficients

x_i and xj represents the coded levels of the independent variables and

Y represents the dependent response variable

To determine the significant differences between the independent variables, analysis of variance (ANOVA) was performed. Multiple regressions and reduced model ($p < 0.05$) were used for the analysis of the experimental data.

- *Verification of the Models:*

To study the adequacy of the constructed model, some random extraction experiments were performed to validate the model predictions. The adequacy of the final reduced models was checked by comparing the actual values with the predicted values.

III. RESULTS AND DISCUSSIONS

➢ *Qualitative Phytochemical Screening*

Preliminary phytochemical analysis of all the solvent extracts revealed the presence of flavonoids, carbohydrates, glycosides, alkaloids, phenolic compounds/tannins, saponins and terpenoids in different extracts. Further, phytochemical analysis of ethanol extract revealed the presence of alkaloids, carbohydrates, flavonoids, glycosides, saponins, phenolic compounds/tannins and terpenoids (Table 1).

Table 1 Phytochemical Screening of *O. corniculata*

S. No.	Test	Petroleum ether extract	Ethyl acetate extract	Ethanol extract
1.	Carbohydrates	-	-	+
2.	Flavonoids	-	+	+
3.	Alkaloids	+	-	+
4.	Glycosides	-	-	+
5.	Saponins	+	+	+
6.	Tannins and Phenol	-	-	+
7.	Terpenoids	+	+	+

➢ *Optimization of UAE by Single-Factor Experiments*

The current study mainly dwelled to optimize the three variables (ultrasonic time, ultrasonic temperature and ethanol concentration) to obtain the maximum phenolic content of the leaves of *Oxalis corniculata*. During the optimization study, minimum and maximum values of variables were identified according to previous researches on the extraction of the phenolic compounds from various treated plant materials [26-29].

- *Effect of Extraction Temperature on TPC:*

The extraction performance has been impacted by the extraction temperature. A greater diffusion coefficient of the compounds of interest resulting in enhanced solubility of these compounds may be due to the increased ultrasonic temperature [30]. It was demonstrated that the UAE was significantly contributed by the extraction temperature. With increase in extraction temperature from 20 to 60°C, the TPC yield increased dramatically (Figure 1). This increase in TPC is indicated since cell wall tissue softening and hydrolysis of the available phenolic compounds in cell wall tissues at high temperatures results in solubilisation of the polyphenols into the solvent [31,32]. The solvent, thus, gains access to the plant matrix hence causing the mass transfer of phenolic compounds into the solvent [33,34]. Nevertheless, at a higher extraction temperature (more than 60°C), the transfer of TPC declined.

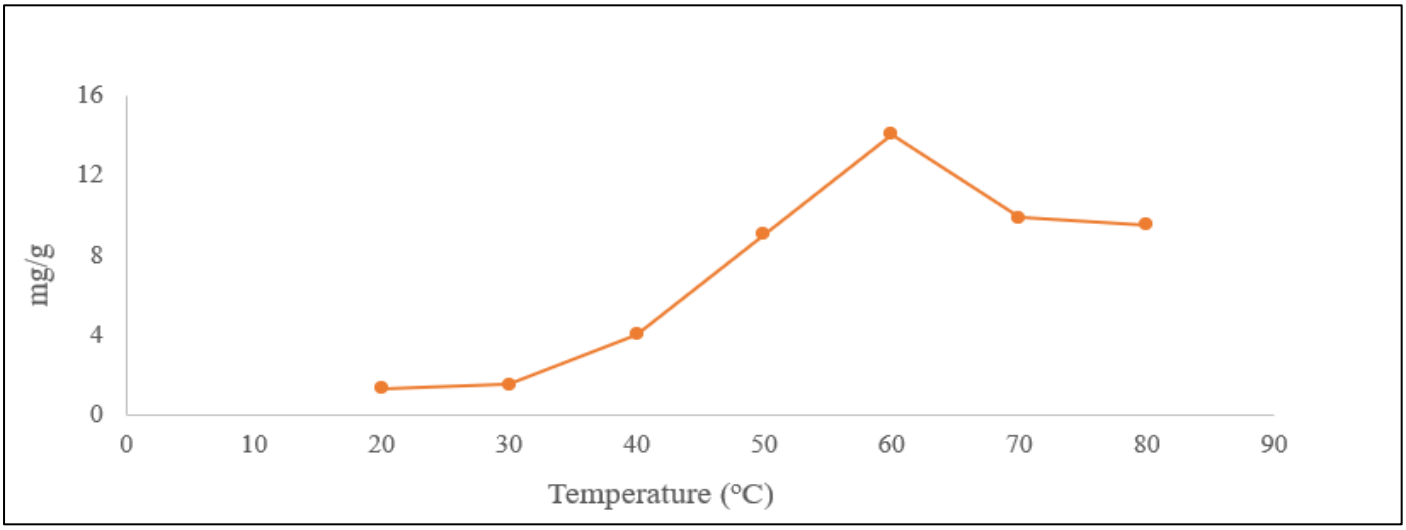

Fig 1 Effect of Extraction Temperature on TPC

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The highest polyphenol content in the conventional extractions has been obtained at temperatures between 60 and 80°C and the best solvents employed in such extractions include ethanol, methanol, and acetone [35-39]. Since the loss of solvents has been recorded at temperatures above 80°C, the studies did not examine extraction temperature above 80-90°C. It has been proved with many studies that the polyphenolic yield lowers when the drying temperature higher than 80°C has been used [41-42]. That is why polyphenols are habitually considered heat-sensitive compounds.

- *Effect of Time of Extraction on the TPC:*

The effect of ultrasound time on TPC has been displayed in Figure 2. The impact of ultrasonication period (10 to 70 min) on TPC was studied with the following conditions: ultrasonic temperature 60°C, methanol concentration 60% (v/v), and liquid–solid ratio of 30 mL/g. The yield of polyphenols (11.82 mg/g) increased with increase in ultrasonication period and reached maximum at 60 min. of extraction, followed by a rapid decline.

The comparatively long extraction period made a favorable impact of the TPC. However, further increase in time of extraction resulted in degradation of polyphenols because of the thermolabile nature of the phenolic compounds. This conclusion is consistent with what was determined by Jeszka-Skowron and Zgoła-Grseven [43] who discovered that prolonged time of *Camellia sinensis* extraction led to a reduction in the content of chlorogenic acid and rutin.

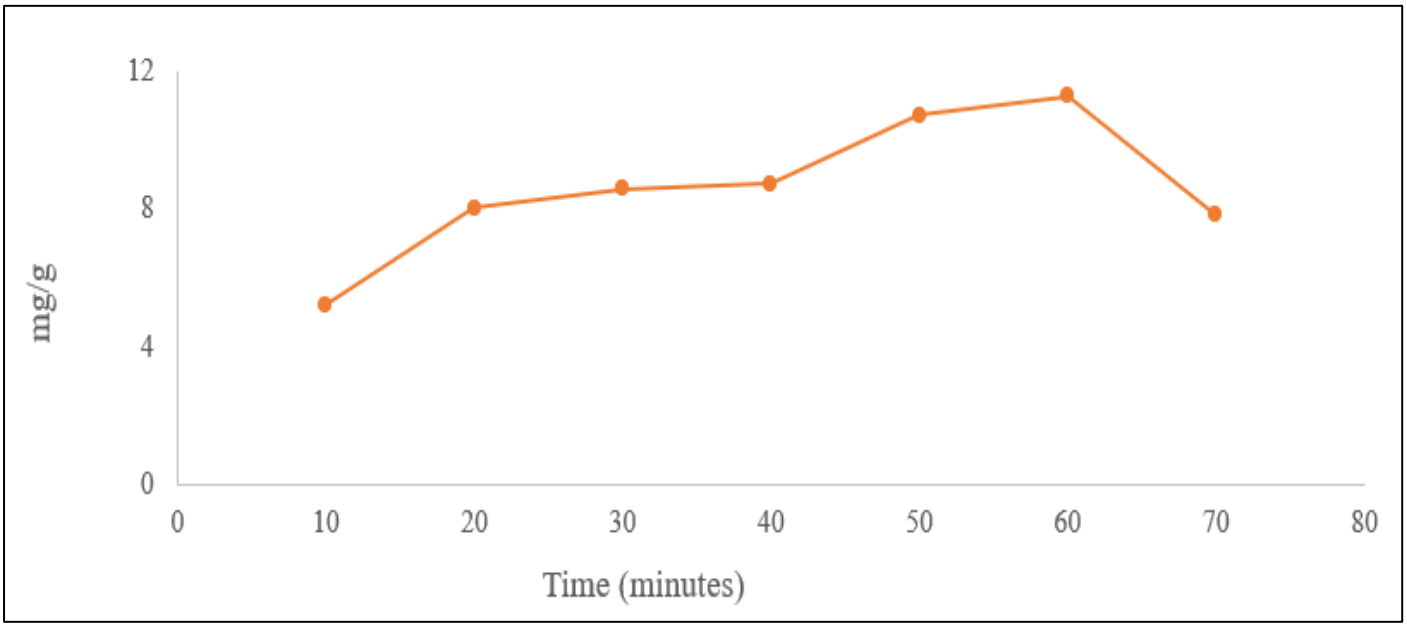

Fig 2 Effect of Time of Extraction on TPC

- *Effect of Ethanol Concentration on TPC:*

The ethanol- water mixture gives an even greater polar atmosphere to the solutes as opposed to the 100% ethanol. Concentration of ethanol also decreases the polarity of the mixture of ethanol and water. Obviously, the phenolic compounds are more attracted to the less polar solvent of extraction compared to water because this condition increases the solubility of phenolic acids and hence leading to the high extraction efficiency. Zuorro et al. [44] stated that phenolic compounds display broad solubility in individual mixture components along with their common behavior to be more soluble in solvents with a lower polarity relative to water.

Aqueous ethanol is a well-known solvent for the extraction of phenolic compounds from plants, where ethanol increases the content of total phenolic compounds by disrupting solute–plant matrix bonds. Moreover, water helps in the swelling of cell material. Therefore, selection of a suitable concentration of ethanol is important for the improvement of the extraction performance. Figure 3 illustrates that the content of total phenols increased with increase in the concentration of ethanol from 30 to 60% but decreased rapidly with ethanol concentration more than 60%. This varying degrees of efficiency of extraction exhibited by different ethanol–water systems might be due to a boost in extraction effectiveness resulting from the addition of a certain amount of water. This increase in effectiveness of extraction is due to enhancement of the polarity of aqueous ethanol with addition of water.

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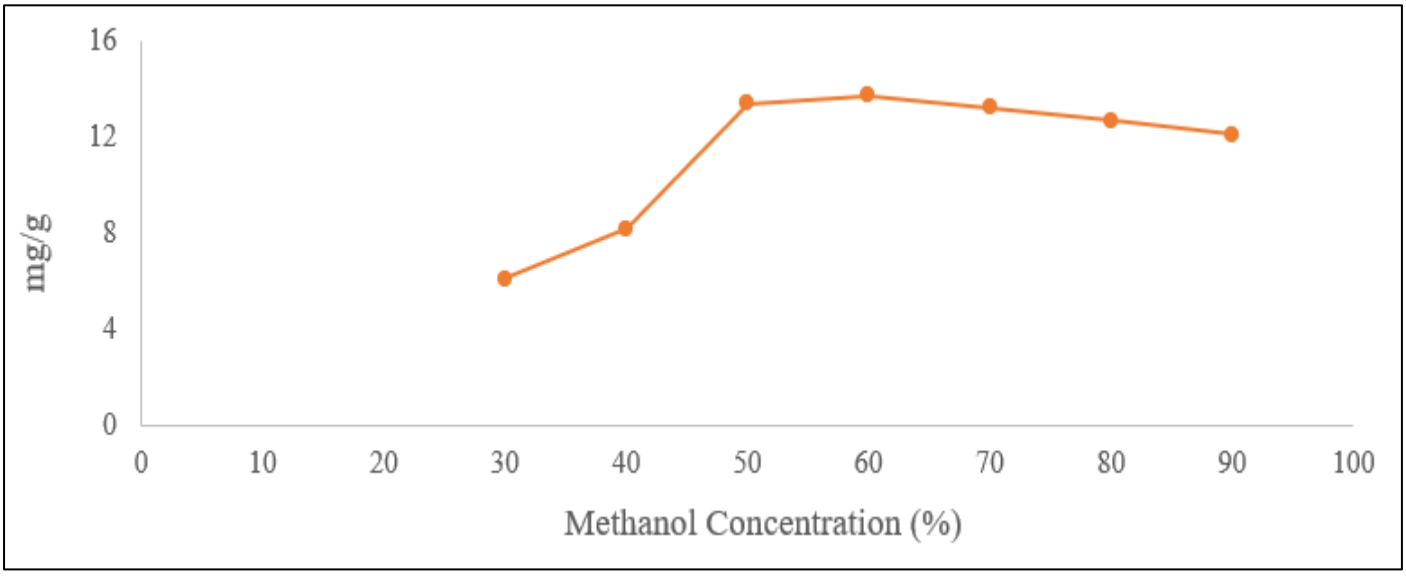

Fig 3 Effect of Ethanol Concentration on TPC

➢ *Model Fitting and Analysis of Variance*

To study the effects of extraction time, extraction temperature and solvent ratio on TPC of the *O. corniculata* leaves, RSM was used with CCRD. Table 2 shows the design matrices of the actual experiments using CCRD and the predicted data for the response variable.

Table 2 Actual and Predicted Values of Extraction Temperatures (A), Extraction Times (B) and Solvent Ratios (Ethanol:Water) (C) for Extraction Conditions of *O. corniculata* Leaves using the CCRD Design

Run	Independent Variables			Response	
	A (°C)	B (min)	C (v/v%)	TPC (mg/g extract)	
				Actual*	Predicted
1	60	60	60	14.30±0.43	14.29
2	43.2	60	60	13.39±0.24	13.40
3	50	50	70	12.67±0.57	12.63
4	60	60	43.2	13.13±0.45	13.12
5	60	60	60	14.34±0.21	14.29
6	60	76.8	60	13.80±0.11	13.83
7	70	70	50	13.00±0.25	13.01
8	76.8	60	60	12.75±0.43	12.78
9	60	60	60	14.34±0.34	14.29
10	70	50	70	12.67±0.31	12.67
11	60	60	60	14.23±0.39	14.29
12	70	70	70	13.01±0.15	12.95
13	60	43.2	60	12.74±0.23	12.75
14	50	70	50	13.80±0.24	13.78
15	60	60	60	14.27±0.18	14.29
16	70	50	50	12.92±0.41	12.90
17	50	50	50	12.75±0.32	12.78
18	60	60	76.8	12.90±0.15	12.95
19	50	70	70	13.81±0.17	13.81

*Values are Expressed as Means_SD (n = 3).

According to Hamzaoui et al. [45] and Jumbri et al. [46], regression model is well fitted when the result is a high correlation with values of R^2 above 0.9. The obtained R^2 values demonstrated that more than 99 percent of the response variable could be characterised by the RSM model. The large values of R^2 representing the responses showed that the CCRD design fitted well into the developed quadratic polynomials models.

Table 3 represents the regression analysis and ANOVA that are used in the model fitting design to analyse whether the terms are statistically significant across all of the responses. A high F value and small p value revealed that the independent variables play a significant role as regards to the respective response variable [47].

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Table 3 ANOVA for Quadratic Model of TPC

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	**7.70**	**9**	**0.8557**	**394.31**	**< 0.0001**	**Significant**
A-Temp.	0.4600	1	0.4600	211.97	< 0.0001	
B-Time	1.41	1	1.41	651.11	< 0.0001	
C-Solvent	0.3356	1	0.3356	166.38	< 0.0001	
AB	0.3916	1	0.3916	180.47	< 0.0001	
AC	0.0036	1	0.0036	1.66	0.2291	
BC	0.3153	1	0.3153	147.06	< 0.0001	
A^2	2.48	1	2.48	1145.12	< 0.0001	
B^2	1.73	1	1.73	797.02	< 0.0001	
C^2	2.72	1	2.72	1251.88	< 0.0001	
Residual	0.0195	9	0.0022			
Lack of Fit	0.0106	5	0.0021	0.9516	0.5341	not significant
Pure Error	0.0089	4	0.0022			
Cor Total	7.72	18				

The predicted value of R^2 (Pre. R^2) indicates the goodness of a regression model in predicting response values; the adjusted R^2 (Adj. R^2) gives the description ability of the regression models with varying numbers of variables. As mentioned by Koocheki et al. [48], Adj. R^2 value greater than 0.9 can be used to describe the adequacy of the model. Moreover, the difference of less than 0.2 between Adj. R^2 and Pre. R^2 shows the efficacy of the model. The Adj. R^2 values obtained in this research were above 0.9 and the difference in Adj. R^2 and Pre. R^2 was less than 0.2 for the response (Table 4). The Lack of Fit analysis also confirmed the validity of the models since an insignificant p value of more than 0.05 provided a confirmatory indication that the model could fit with the actual data [49].

Table 4 Fit Statistics

	Standard Deviation	Mean	R^2	Adjusted R^2	Predicted R^2	Adeq. Precision	Lack of Fit p-value
TPC	0.0466	13.41	0.9965	0.9949	0.9870	49.1677	0.5341

Three-dimensional (3D) response surface images can show the mutual effect of any two independent variables on the dependent variable when all other independent variables are taken to zero and the shape of 3D response surface plots determines the degree of influence [50,51]. The resulting impact of a combination of temperature and time had a positive influence (the increase) on the TPC. When temperature increases over a brief time (Figure 4), the plant matrix is rendered fragile and, the solvent enters into the cell leading to a mass exchange of soluble substances into the solvent out of the matrix [33,52].

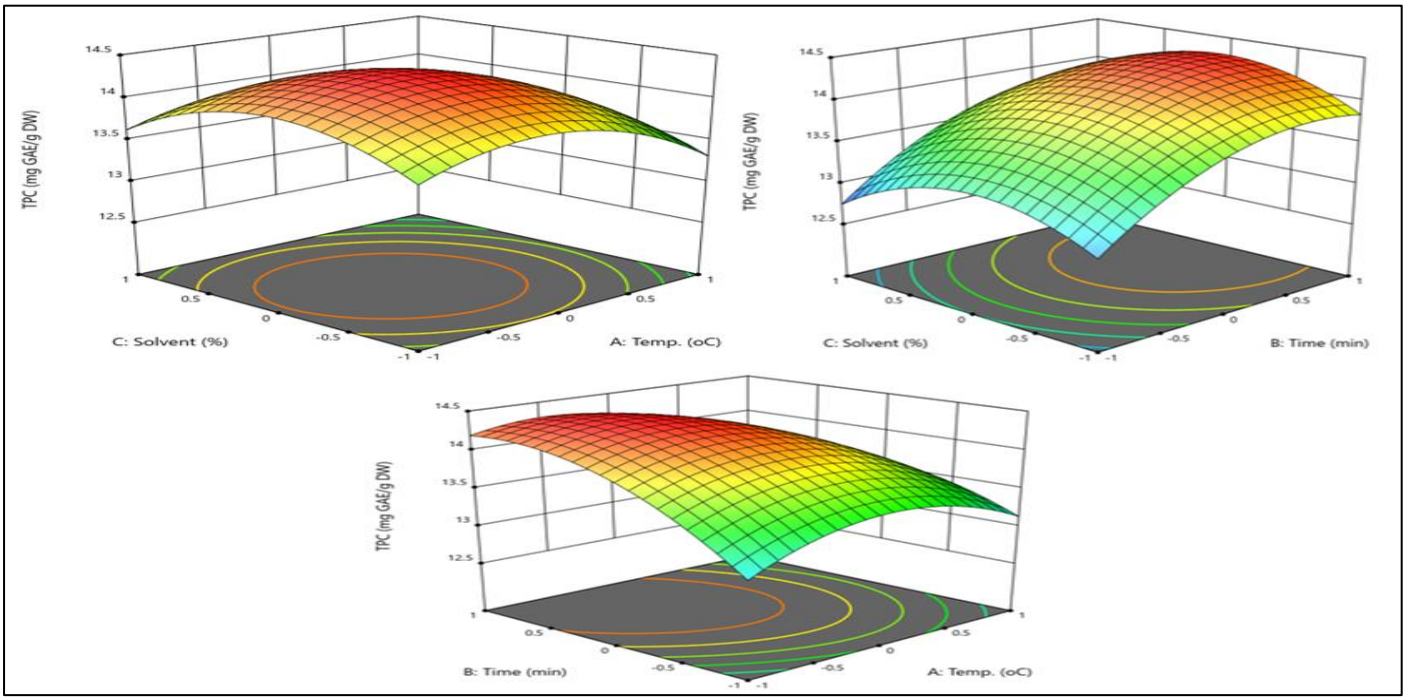

Fig 4 Response Surface 3D Plots of TPC.

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➢ *Validation of the Optimized Model*

The final optimization process for TPC by RSM yielded optimum extraction parameters as extraction time of 62.66 minutes, extraction temperature of 55.29°C and the ethanol concentration of 60.28%. 14.373 mg g^{-1} was the theoretical TPC yield under the optimized UAE conditions. The confirmatory experiments were conducted under the optimum extraction conditions in order to validate the reliability of the prediction model. Confirmatory tests provided a satisfactory result that the TPC was 14.23±0.07 mg g^{-1}, which was well-matched to the theoretical result.

IV. CONCLUSION

This research has demonstrated that RSM could be implemented successfully to optimise the extraction process of *O. corniculata* leaves and helps to explain the correlation between the independent variables and response variables better. ANOVA was used to verify the model in a statistical manner. The actual values were in good correspondence with the predicted values, since the values of RSE were less than 0.2 percent under the optimum conditions. The results showed that all the independent variables did significantly affect ($p<0.05$) the response, which indicated that all the extraction parameters used in this study were necessary in the optimization process. The R^2 values greater than 0.9 indicating that the quadratic polynomial models derived were good enough to be utilized in analyzing the interactions of the parameters (independent variables and response). The temperature, extraction time, and solvent ratio with the best conditions, which were provided by the RSM would be utilized in future upscale extractions of *O. corniculata* leaves to make the extractions economically feasible.

➢ *Competing Interests*

There are no competing financial or non-financial interests to declare.

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