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OPTIMIZATION OF ULTRASOUND-ASSISTED EXTRACTION OF PHENOLIC COMPOUNDS FROM *AMMI VISNAGA* USING RESPONSE SURFACE METHODOLOGY

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ABSTRACT: In this study, response surface methodology (RSM) was used to optimize ultrasound-assisted extraction (UAE) conditions for obtaining the maximum yield and content of phenolic compounds of *Ammi visnaga* extracts (EAV**)**. Three independent variables including ethanol concentration (%), extraction time (time) and solvent-to-material ration (mL/g) were studied. The results showed that the optimal UAE condition was obtained with an ethanol concentration of 76%, an extraction time of 36 min and a solvent-to-material ratio of 13 mL/g for total phenols. Ethanol concentration, extraction time and solvent-to-material ratio was respectively 79%, 38 min and 11 mL/g for the maximum yield. The experimental values under optimal conditions were in good consistent with the predicted values, confirming the suitability of the model employed and the success of RSM for optimization of the extraction conditions.

INTRODUCTION: *Ammi visnaga (A. visnaga)* has many English names, including Khella, visnaga, Bisnaga, and Toothpick weed. It is a member of the Apiaceae (Umbelliferae) family; widely and wildly distributed in Asia, Europe and North Africa [1, 2]; especially in Egypt, Morocco and the Islamic Republic of Iran [3]. It has antispasmodic activity and is recommended for stomach cramps, kidney stones, kidney colic and pain in the urinary tract [4]. It is also used as a remedy against asthma, angina, cardiovascular diseases, diabetes and vitiligo [5]. The khiline, visnagine, and visnadine are the principal actives of the fruits of *A. visnaga*, and they are used in the pharmaceutical industry [6].

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The level of compounds in the dry fruits varies widely depending on genetic factors and environmental conditions [7]. Different methods, including refluxing, boiling, heating and Soxhlet extraction, have been used for the extraction of phenolic compounds; however, the disadvantages are the loss of phenols due to oxidation, hydrolysis, and ionization during extraction as well as the long extraction time [8]. Recently, various new extraction techniques have been developed for the extraction of the phenolic compounds from plants, including microwave-assisted extraction (MAE) [9], ultrasound-assisted extraction (UAE) [10], accelerated solvent extraction (ASE) [11] and supercritical fluid extraction (SFE) [12]; Among these, UAE is an inexpensive, simple and efficient alternative to conventional extraction technique.

The enhancement of extraction using ultrasound is mainly attributed to acoustic cavitations produced in the solvent [13, 14]. Many factors such as solvent concentration, extraction temperature, solvent-to-

solid ratio, solvent pH and pressure may significantly influence the extraction efficiency, antioxidant activity and phenolic content [15, 16].

Hence, it is necessary to optimize the extraction conditions to obtain the higher yield and phenolic content.

To optimize the extraction conditions, including the concentration of solvent, extraction time and solvent-to-material ratio, response surface methodology (RSM) has been widely used. RSM has been applied to optimize UAE of phenolic compounds in many studies [11, 17], to the best of our knowledge, there are no reports yet about the application of RSM on UAE optimization for the extraction of phenolic compounds from *A. visnaga*.

RSM can be used to evaluate the effects of multiple factors and their interactions with one or more response variables [18, 19]. Different RSM methods such as Box-Behnken design (BBD), central composite design (CCD) and three-level full factorial design (TFFD) have been widely used [20]. The advantage of RSM is the reduced number of experimental trials needed to evaluate multiple parameters and their interactions.

In this work, the main objective was to investigate the extraction variables (extraction time, Ethanol concentration and solvent-to-material ratio) and optimize these variables values by RSM for maximization of extraction yield and content of total phenolic.

MATERIALS AND METHODS:

Vegetal Material: *A. visnaga* was collected from the Taounate region of Morocco in July 2017. The botanical identification of the species was carried with the laboratory of Biotechnology and Preservation of Natural Resources (BPNR), Sidi Mohamed Ben Abdellah University, Fez, Morocco.

Ultrasounds Assisted Extraction: The plant drug has been crushed and mixed with a predetermined volume of ethanol (%) and then they are placed in a 250 mL Erlenmeyer flask. The extractions were performed at different solvent percentages, amount of material and for different periods in an ultrasonic bath (45Hz; 100W). After extraction, the mixture was filtered through Whatman paper, and the solvent was removed using vacuum steam rota.

Experiment Design: Response surface methodology (RSM) was used for investigating the influence of three independent variables on total phenols and yield of EAV. The main factors are affecting the extraction efficiency including the ethanol concentration (%, X_1), extraction time (min, X_2) and the solvent-to-material ratio (mL/g, X_3). The temperature was not considered in this present work because the sample was kept at room temperature to avoid the degradation of temperature-sensitive compounds.

In the study, the experiments were performed on the Box-Behnken Design (BBD). Three variables were used to optimize the best combination of extraction variables for *A. visnaga* yield and total phenol content.

The complete design was carried out in random order and consisted of 17experiment including five replicates at central point **Table 1**. The data from BBD were analyzed by multiple regressions to fit the following quadratic polynomial model Equation1:

$$Y = \beta_0 + \sum b_i X_i + \sum b_{ii} X_i^2 + \sum b_{ij} X_i X_j$$

Where Y is the predicted response, β_o is a constant *bi*, *bii* and *bij* are the linear, quadratic and interactive coefficients of the model, respectively. Accordingly, *Xi* and *Xj* represent the levels of the independent variables, respectively. The quality of the fitted model was expressed by the coefficient of determination (R^2).

Determination of the Total Phenolic Content: The total phenols of the extract *A. visnaga* were estimated using the Folin-Ciocalteu method [21]. This method allows knowing the total polyphenolic content of a given sample. The plant extract (100 µL), suitably diluted, is introduced into a test tube initially containing 6 mL of distilled water, then 500 µL of the Folin reagent is added, and the mixture is stirred. After 5 min, a solution of 20% Na_2CO_3 (1.5 mL) is added while stirring.

The solution is adjusted to 10 mL with distilled water. After 2 h of incubation, at room temperature, the absorbance is measured with a white made from distilled water using a spectrophotometer UV-Visible kind Selecta at 760 nm. A calibration curve with different concentrations of gallic acid was

plotted. The total phenol content in the extract was expressed in milligram equivalent of gallic acid per gram of extract (mg EGA/g extract), all samples were analyzed in triplicate.

TABLE 1: BBD EXPERIMENTAL DESIGN WITH THE INDEPENDENT VARIABLES

Rand	Ethanol (X_1) %	Extraction time (X_2) min	Solvent-to-material (X_3) mL/g	Yield %	TPC mg (EGA/g extract)
1	40	20	20	12.40	119.34
2	80	20	20	15.20	155.80
3	40	40	20	13.50	138.56
4	80	40	20	17.50	168.50
5	40	30	10	19.00	180.80
6	80	30	10	21.00	195.30
7	40	30	30	8.00	94.16
8	80	30	30	10.80	100.43
9	60	20	10	17.00	168.50
10	60	40	10	18.00	176.50
11	60	20	30	7.23	76.10
12	60	40	30	9.00	98.23
13	60	30	20	14.50	140.19
14	60	30	20	14.23	140.00
15	60	30	20	14.20	140.00
16	60	30	20	14.00	140.00
17	60	30	20	14.00	140.00

Statistical Analysis: The experimental results of the response surface design were analyzed using Nemrowd software. *P*-values <0.05 were considered to be statistically significant. All experiments were conducted in triplicate unless otherwise noted in the text.

RESULTS AND DISCUSSION:

Fitting the Model: To obtain a more realistic mode, it was necessary to investigate the process variables. Preliminary trials enabled the range of ethanol concentrations (40-80%), extraction time (20-40 min) and the solvent-to-material ratio (10-30 mL/g) to be fixed.

As **Table 2** shows, the analysis of variance (ANOVA) of extraction yield and total phenolic indicated that experimental data had a determination coefficient (R^2) of 0.994 and 0.985 respectively, which indicates that only 0.6% of the total variations were not explained by model for extraction yield and 1.5% for total phenolic indicating the good representation of the variability of the parameters by the models.

R^2 adj (adjusted determination coefficient) is the correlation measure for testing the goodness-of-fit of the regression equation [22, 23].

TABLE 2: ANALYSIS OF VARIANCE FOR THE FITTED QUADRATIC POLYNOMIAL MODEL OF EXTRACTION YIELD AND TOTAL PHENOLIC OF A. *VISNAGA* RESPECTIVELY

Source	Sum of squares	Degree of freedom	Mean square	P-value
Regression	231.3150	9	25.70	<0.001
Residual	1.4576	7	0.2082	
Validity	1.2877	3	0.4292	2.45
Pure error	0.1699	4	0.0425	
Total	232.77	16		

R^2 = 0.994; R^2 adj = 0.986; R^2 pred = 0.910

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For a good statistical model, the adjusted determination coefficient (R^2 adj) should be close to R^2. As shown in **Table 2**, R^2 adj (0.986 for extraction yield and 0.965 for total phenolic of *A. visnaga*) were close to R^2. Moreover, R^2 pred (0.910 for extraction yield and 0.920 for total phenolic) is in reasonable agreement with R^2 adj and confirms that the model is highly significant.

TABLE 3: ESTIMATED REGRESSION MODEL OF RELATIONSHIP BETWEEN RESPONSE VARIABLE (YIELD AND TPC OF *A. VISNAGA*) AND INDEPENDENT VARIABLES (X1, X2, X3)

Variable	P-value	
	Yield	TPC
ß$_0$	< 0.001 ***	< 0.001 ***
X_1	< 0.001 ***	< 0.001 ***
X_2	0.0451 ***	< 0.001 ***
X_3	< 0.001 ***	< 0.001 ***
X_1^2	0.0302 ***	< 0.001 ***
X_2^2	0.207 **	< 0.001 ***
X_3^2	0.271 **	< 0.001 ***
X_1X_2	4.36 *	< 0.001 ***
X_1X_3	12.4	< 0.001 ***
X_2X_3	13.5	< 0.001 ***

It can be seen in **Table 3** that extraction yield was affected most significantly by ethanol (X_1) (p<0.05) and solvent to the material (X_3) followed by extraction time (X_2) (p<0.05). It was evident that all the quadratic parameter (X_1^2) was significant at the level of p<0.05 whereas two quadratic parameters (X_2^2, X_3^3) and interaction quadratic parameters were insignificant (X_1X_2, X_2X_3, X_1X_3) (p>0.05).

The ANOVA outcome shown in **Table 3** revealed that the first order terms of independent variables (X_1, X_2 and X_3) quadratic terms (X_1^2, X_3^2 and X_2^2) and the interaction term (X_1X_2, X_1X_3 and X_2X_3 significantly affected the content of total phenolic of *A. visnaga* (p<0.05).

Analysis of Response Surface:

Effect of Extraction Parameters on Yield Extraction: The regression equation was graphically represented by 2D+3D response surface from two-dimensional response surface curves shown in **Fig. 1A**, **1B**, **1C**, the effect of the independent variables and their mutual interaction on the extraction yield of *A.visnaga* can be seen. **Fig. 1A** shows the interaction between ethanol concentration (X_1) and extraction time (X_2) on the extraction yield. Increase in ethanol concentration from 51 to 71% with extraction time from 20 to 32 min enhanced the extraction yield. While with an increase of ethanol concentration over 75% there was a gradual decline in the response and extraction time over 32 min did not show any obvious effect on extraction yield. This could be explained by the increasing extraction time accelerating chemical decomposition of bioactive compound in the extract process, resulting in lower extraction yield [24].

Fig. 1A shows that extractions yield of *A. visnaga* could reach a peak value (16.96%) with 71% ethanol concentration and 32 min extraction time.

Fig. 1B indicates the effect of ethanol concentration (X_1) and solvent to the material (X_3) on the extraction yield of *A. visnaga*. It can be seen in **Fig. 1B** that by varying the ethanol concentration from 56 to 79% with decrease solvent to material from 29 to 10 mL/g, the extraction yield of target compounds increased with increase in ethanol concentration and a decrease of solvent to material.

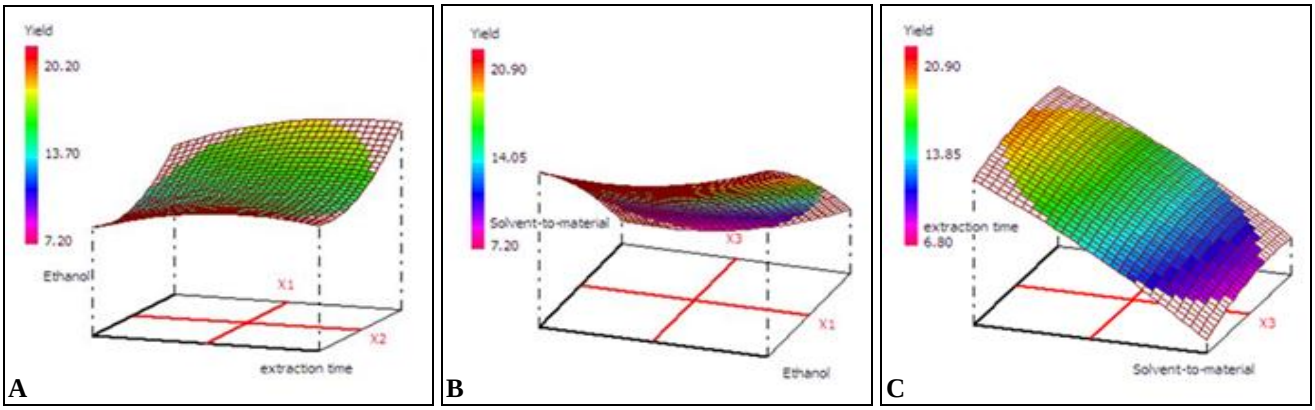

FIG. 1: RESPONSE SURFACE PLOT AND CONTOUR PLOT OF ETHANOL CONCENTRATION AND EXTRACTION TIME (A), SOLVENT TO MATERIAL AND ETHANOL CONCENTRATION (B), EXTRACTION TIME AND SOLVENT TO MATERIAL (C) AND THEIR MUTUAL INTERACTIONS ON THE YIELD OF *A. VISNAGA*

As shown in **Fig. 1B** that extraction yield of *A. visnaga* could reach a peak value (18.77%) with 79% ethanol concentration and 11 mL/g of solvent to the material.

Fig. 1C presents the interaction of extraction time and the solvent-to-material ratio. It was found that maximum yield (18.30%) was achieved when the extraction time was 38 min and the solvent-to-material ratio was 11 mL/g.

Effect of Extraction Parameters on Total Phenol Content: Fig. 2A, **2B,** and **2C** present the response surface and contour plots for the influences of extraction parameters on total phenols content. As shown in **Fig. 2A** that maximum total phenols extraction (155.12 mg EGA/g extract) could be achieved when the ethanol concentration and extraction time 73% and 31 min respectively. As the extraction of phenolic compounds depends largely on the polarity of solvents and compounds, a single solvent might not be effective for the extraction of a bioactive compound.

Hence, a combination of alcohol with water is more effective in extracting phenolic compounds than alcohol alone [25]. The total phenols yield increased with an increase in ethanol concentration from 50% to 76%. This is probably due to the increased solubility of phenolic compounds in the mixture of ethanol and water. The findings obtained from our study are in good agreement with [26, 27].

In this study, however, the total phenols yield decreased when the ethanol concentration was above 75.30%. The total phenols yield increased with prolonged extraction time from 20 to 40 min. This observation was understandable because an extended extraction time favors the extraction of phenolic compounds.

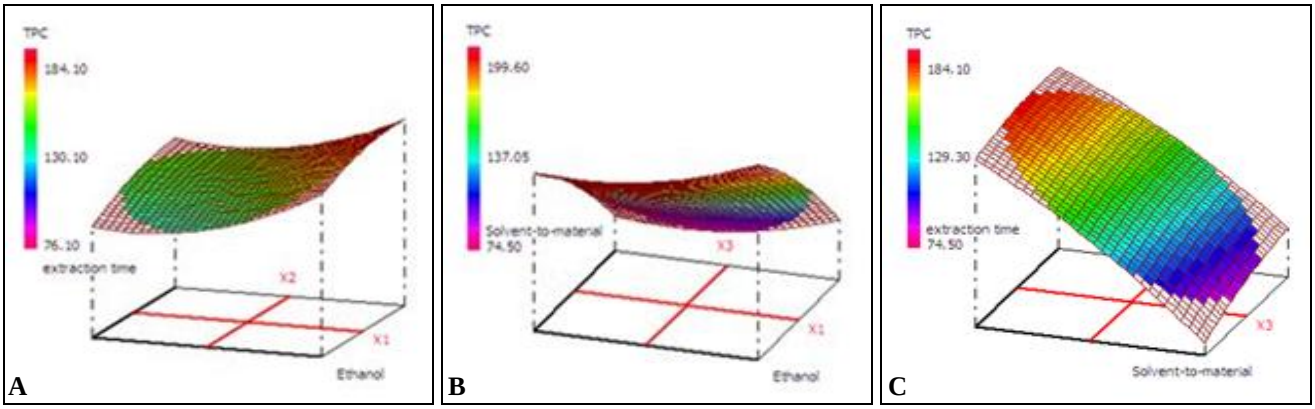

FIG. 2: RESPONSE SURFACE PLOT SHOWING THE COMBINED EFFECT OF ETHANOL CONCENTRATION AND EXTRACTION TIME (A), SOLVENT-TO-MATERIAL RATIO AND ETHANOL CONCENTRATION (B) SOLVENT-TO-MATERIAL RATIO AND EXTRACTION TIME (C) ON TOTAL PHENOLS CONTENT OF *A. VISNAGA* EXTRACTS

Fig. 2B presents the interaction of ethanol concentration and solvent-to-material ratio. The increased extraction yield of total phenols was observed with a decreased solvent-to-material ratio from 20 to 10. This is probably due to the fact more solvent can enter cells while more phenolic compounds can permeate into the solvent under the low material par rapport solvent conditions [28]. It can be concluded from **Fig. 2B** that maximum total phenols extraction (178.58 mg EGA/g extract) could be achieved when the ethanol concentration and solvent-to-material ratios were 76% and 13mL/g.

Fig. 2C presents the interaction of extraction time and the solvent-to-material ratio. It was found that the maximum total phenols yield (174.50 mg EGA/g extract) was achieved when the extraction time was 36 min and the solvent-to-material ratio was 11 mL/g.

Verification of Predictive Model: The maximum predicted and experimental values of the extraction yield and total phenolic of *A. visnaga* are shown in **Table 4**. Three optimal conditions were developed for the two responses, which were ethanol concentration 78%, 38 min and 12 ml/g *via* the optimum conditions, the corresponding predicted responses of TPC and yield were 199.65 mg GAE/g and 20.95%, respectively. The experiments were run following the recommended optimum conditions for two responses, to test the adequacy of the surface response model in predicting the optimum response values.

The observed values for TPC and yield were 197.85 ± 0.4 mg GAE/g of extract and 20.10 ± 0.2% respectively. The predicted extraction yield and total phenolic of *A. visnaga* were close to this experimental value which indicates that the proposed model is reliable.

TABLE 4: OPTIMUM CONDITIONS AND THE PREDICTED AND EXPERIMENTAL VALUE OF RESPONSE AT THE OPTIMUM CONDITIONS

	Ethanol X_1	Extraction time X_2	Solvent-to-material X_3	Extraction Yield %	TPC (mg EGA/g extract)
Optimum conditions	78%	38min	12	20.95 ± 0.5	199.65 ± 0.03
Modified conditions	78%	38min	12	20.10 ± 0.3	197.85 ± 0.05

CONCLUSION: A UAE method was employed to extract the phenolic compounds of *A. visnaga*. In this study, RSM was first utilized to estimate and optimize three variables (ratio of solvent to raw material, extraction time and ethanol %) for obtaining maximum yield and total content phenolic with less experimental trials. The optimal extraction conditions for the maximum yield and content of total phenolic were as follows: 12 mL/g ratio of solvent to raw material, 38 min extraction time and 78% ethanol. Under these conditions, the predicted yield and content of total phenolic by the model was 20.95% and 199.65 (mg EGA/g extract) respectively, whereas the actual yield of *A. visnaga* was 20.10% and values of total phenolic were 197.85 (mg EGA/g extract) in adjusted optimal conditions.

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CONFLICT OF INTEREST: We declare that we have no conflict of interest.

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