

Optimization of Phenolic and Flavonoid Extraction in Lavandula Angustifolia using Ultrasonic Assistance Extraction

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ABSTRACT

Lavender contains active compounds such as flavonoids, tannins, coumarins, phytosterols, and minerals, which possess antioxidant properties and pharmacological potential. This study optimized the extraction process of lavender flowers to maximize bioactive phenolic and flavonoid yields. Ultrasonic-assisted extraction (UAE) was employed, and optimization was conducted using a Box-Behnken design in Design Expert 13.0.5.0 software. The influence of ethanol concentration, liquid-solid ratio (LSR), and extraction time on total phenolic content (TPC) and total flavonoid content (TFC) was evaluated. Results revealed that LSR significantly impacted the responses. Optimal conditions were determined as an LSR of 50 mL/g, extraction time of 26 minutes, and ethanol concentration of 26.12%. Validation under these conditions yielded a TPC of 152.26 mg GAE/g DE and a TFC of 68.59 mg QE/g DE, with percentage errors of -7.7% and 3.5%, respectively, demonstrating excellent agreement with the predicted values.

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1. INTRODUCTION

Lavender (*Lavandula angustifolia*) is a plant that possesses a unique and gentle fragrance that induces relaxation [1]. Lavender has active ingredients, including flavonoids like phenolic compounds, anthocyanins, phytosterols, tannins, coumarins, and mineral compounds. Flavonoids and phenolic compounds possess antioxidant properties and have numerous pharmaceutical applications [2] [3]. These substances are crucial in combating free radicals by assisting the body in mitigating oxidative damage that may result in numerous degenerative diseases, including cancer, diabetes, and cardiovascular disease [4] [5]. Consequently, the advancement of effective techniques for isolating bioactive chemicals from lavender is essential for pharmaceutical and food research.

Secondary metabolites can be obtained using chemical separation techniques, particularly through extraction methods. Traditional extraction techniques frequently exhibit drawbacks including prolonged extraction duration, diminished yield, and excessive solvent usage [6]. Therefore, the development of more effective approaches is essential. Ultrasonic extraction, or Ultrasonic-Assisted Extraction (UAE), is a contemporary technology that provides high efficiency in the extraction of bioactive chemicals from natural materials. In the UAE method, ultrasonic vibrations produce cavitation effects that affect plant cell walls and membranes, hence improving the solvent's infiltration into the cell membrane and increasing the mass transfer rate of the tissue and active chemicals from the cell to the solvent [7] [8]. The UAE approach conserves time, energy, and solvent while enhancing the efficiency of active chemical recovery from the extracted material [9] [10]. Based on the research conducted by Fauziyah et al., the extract yield obtained through the UAE method reached 69.286%, which is higher than the maceration method, which yielded only 43.176% [11].

Optimizing the extraction method is crucial for optimizing the output of advantageous bioactive chemicals, such as phenolic and flavonoid compounds, in lavender, recognized for their significant antioxidant potential. UAE method, enhanced by experimental designs like the Box-Behnken Design (BBD), facilitates the efficient and precise identification of optimal conditions by accounting for the interactions among variables such as extraction time, solvent volume, and solvent concentration. It also aids in reducing the quantity of experiments necessary, hence enhancing efficiency regarding time and resources [12] [13]. This method ensures optimal conditions with a more scientific, structured and controlled approach, thereby increasing efficiency and accuracy in research. BBD is used because it has various advantages over Central Composite Design (CCD) when applying three variable factors yet can achieve comparable results. BBD ensures that extreme test points or axial points are not included in the design [14].

BBD approach was employed to optimize the lavender extraction procedure in the UAE, as indicated by this description. A series of studies was therefore conducted. Total Phenolic Content (TPC) and Total Flavonoid Content (TFC) are the primary responses that are assessed as indicators of the presence of bioactive compounds. This research aims to substantially enhance the development of effective extraction techniques and augment the

potential use of lavender as a source of natural antioxidants. By improving the yield of valuable phytochemicals from lavender, the findings support its enhanced application in the pharmaceutical, nutraceutical, and food industries. Moreover, the integration of BBD in optimizing UAE conditions demonstrates a novel and practical combination that has not been extensively reported in prior studies involving lavender, reinforcing the scientific novelty and practical significance of this research.

2. RESEARCH METHODS

2.1 Materials and Tools

The research employed lavender flowers obtained from Cirebon, West Java. The solvents utilized in this study are distilled water and ethanol, accompanied by a range of reagents for the analysis of phenolic compounds and flavonoids. This study employs a range of ultrasound-assisted extraction tools alongside UV-Vis spectrophotometric analysis.

2.2 Experimental Procedure

Sample Preparation

The lavender is collected in a desiccated form, subsequently ground into a fine powder through a thorough mixing process, and then subjected to sieve to achieve a refined powder consistency [15].

Ultrasound assisted extraction

Lavender flowers were extracted utilizing the UAE technique, as described by Akmal et al., with some modifications [16]. The extraction utilized ethanol and distilled water as solvents. A total of 1 gram of simplisia was combined with a specific volume of solvent to produce various samples. A 100 ml glass bottle containing the sample and solvent was positioned in a sonicator bath operating at a constant ultrasonic frequency of 40 kHz, with an ultrasonic power of 120W, and maintained at a temperature of 50°C. The response surface methodology (RSM) experimental design established several combinations of time, ethanol concentration, and solvent ratio. The ranges for each independent variable are shown in Table 1.

Table 1. Levels of each of the independent variables employed in the Box–Behnken design

Independent Variables	Level		
	-1	0	+1
Ethanol Concentration (%)	0	48	96
Liquid-solid Ratio (ml/g)	10	30	50
Extraction Time (min)	5	17.5	30
Dependent Variables	Constraints		
TPC (mg GAE/g DW)	Maximize		
TFC (mg QE/g DW)	Maximixe		

Response Analysis

The analysis of lavender flower extracts (LFE) focused on determining the total phenolic content and total flavonoid content through UV-Vis spectrophotometry. TPC was assessed utilizing the Folin-Ciocalteu (FC) method, as described by Akmal et al [17]. TFC was assessed via the AlCl_3 technique, as described by Werdiningsih et al [18], with certain modifications applied.

Design Experiment

The optimal set of process parameters for the extraction of LFE was found using BBD for UAE process optimization. The variables examined included ethanol concentration (A), liquid-solid ratio (B), and extraction duration (C), while the responses measured were TPC TFC [19]. The analysis of data was conducted utilizing Design-Expert v13 software. The layout featuring three levels and three independent variables is illustrated in Table 1.

3. RESULTS AND DISCUSSION

3.1 Optimization of the extraction process

The extraction of lavender is affected by multiple circumstances and conditions, which considerably influence the bioactive qualities of the recovered components. The principal objective of this study was accomplished through the extraction of lavender using an ultrasonic-assisted extraction method.

BBD was employed to optimize and ascertain the maximum TPC and TFC in LFE. Utilizing three independent variables: ethanol concentration (%), LSR (mL/g), and extraction duration (minutes). In accordance with the experimental design, a total of 15 experiments were conducted, including 3 center points. The results for the phenolic and flavonoid contents from each experiment are detailed in Table 2.

Tabel 2. Box Behnken design of three variables with their observed responses of lavender flower extraction

RUN	Ethanol Concentration (%)	LSR (mL/g)	Extraction Time (min)	TPC (mg GAE/g DE)	TFC mg QE/g DE
1	48	30	17.5	61,88 ± 0,07	50,59 ± 0,00
2	48	30	17.5	57,33 ± 0,08	61,45 ± 0,00
3	96	30	5	27,50 ± 0,00	35,22 ± 0,07
4	0	50	17.5	163,99 ± 0,20	58,99 ± 0,96
5	48	10	5	7,02 ± 0,02	19,20 ± 0,10
6	48	50	30	161,75 ± 0,23	64,68 ± 0,00
7	0	30	30	59,68 ± 0,04	39,21 ± 0,04
8	48	10	30	7,03 ± 0,00	20,73 ± 0,08
9	0	10	17.5	6,59 ± 0,01	17,08 ± 0,01
10	48	30	17.5	64,46 ± 0,04	58,10 ± 0,00
11	48	50	5	141,95 ± 0,04	59,11 ± 0,10
12	96	30	30	37,18 ± 0,01	44,05 ± 0,19
13	96	10	17.5	6,91 ± 0,01	13,72 ± 0,02

RUN	Ethanol Concentration (%)	LSR (mL/g)	Extraction Time (min)	TPC (mg GAE/g DE)	TFC mg QE/g DE
14	96	50	17.5	78,38 ± 0,00	66,17 ± 0,53
15	0	30	5	60,12 ± 0,05	31,37 ± 0,47

* Each response is the average of triplicate with standard error

The response variables assessed in UAE extractions include TPC and TFC content. The technique utilized in the UAE process exploits cavitation, producing bubbles that attain elevated pressure and temperature within the substrate. The subsequent rupture of these bubbles leads to improved extraction of components through cell disruption, thereby promoting efficient extraction of the desired components. The application of ultrasonic waves induces acoustic cavitation, leading to localized fragmentation and erosion [20]. The combined influences of the three chosen variables on TPC and TFC are illustrated in Figures 1 and 2 and are summarized in Table 3. The analysis involved setting one variable at level 0 while examining the effects of the remaining two variables on the response values. Figure 1A-C illustrates the impact of the variables on TPC, while Figure 2A-C demonstrates the influence of the variables on TFC. The blue and red areas in these figures illustrate the results of low and high concentrations of TPC and TFC, respectively. The yields of TPC and TFC rise as LSR increases.

The obtained extracts demonstrated an elevation in TPC and TFC concentrations corresponding to the increasing LSR factors. With an increase in solvent volume, the transfer of mass is boosted by an elevated concentration gradient and improved solute-solvent interactions. This aligns with the study by Sasongko et al [21], which indicates that solvent volume significantly influences the enhancement of total extracted phenolics. This aligns with the findings by Yulianingtyas et al [22], which indicate that an increased volume of solvent enhances flavonoid extraction. The greater the solvent volume, the more effectively cell walls and membranes are disrupted due to the pressure differential between the intracellular and extracellular environments, resulting in an increased dissolution of flavonoids within the cytoplasm. The values of TPC and TFC are influenced by the concentration of ethanol. The solvent is crucial in the extraction procedure [23]. Excessive ethanol content can diminish the solubility of the water-ethanol mixture, as phenolics and flavonoids necessitate a balance between the polarities of water and ethanol [24] [25]. Phenolic compounds and flavonoids typically exhibit high solubility in polar solvents like ethanol and water due to their glycosidic bonding with sugars and their common presence in cell vacuoles [26] [27] [28]. Conversely, an excessively prolonged extraction period will provide adverse consequences. Prolonged extraction time may result in the breakdown of specific active chemicals, particularly those sensitive to temperature or pH [29] [30].

Figure 3 illustrates a comparison between the actual and projected outcomes of rosemary extraction for each response, derived from a quadratic model utilizing the Box-Behnken Design (BBD). The graph demonstrates that the predicted and actual data align closely with the 45° line, indicating a robust connection between the model and the experimental data.

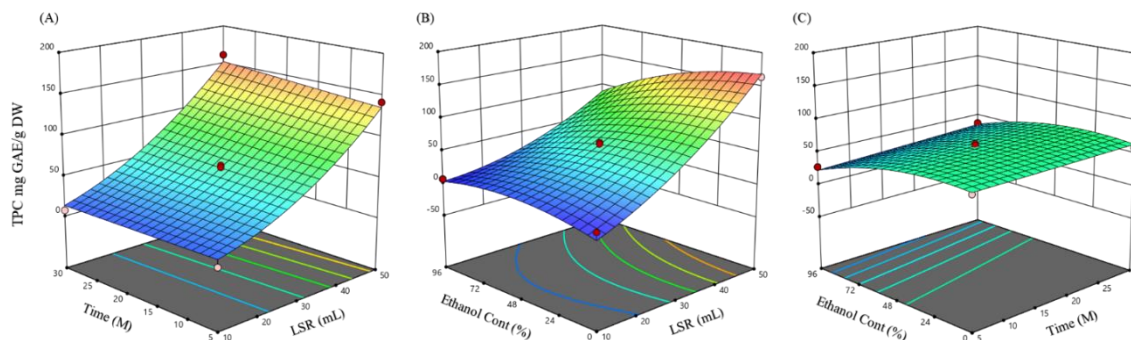


Figure 1. Effect of independent variables (A) LSR and extraction time, (B) LSR and ethanol concentration, and (C) extraction time and ethanol concentration on the total phenolic content value.

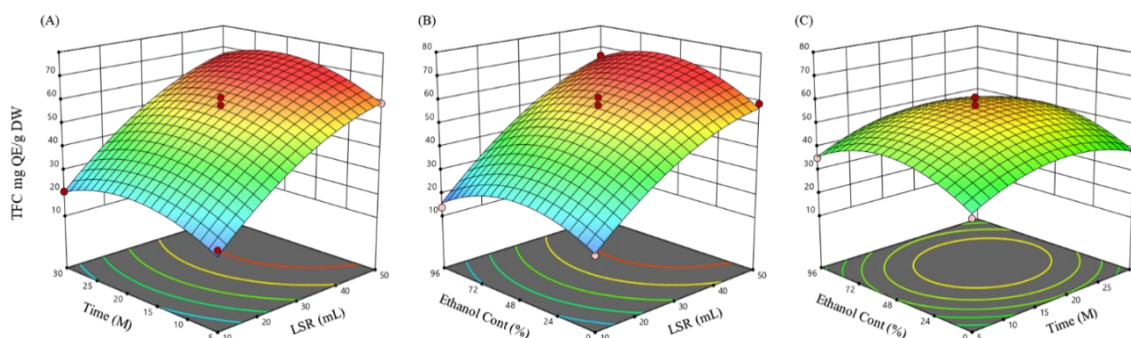


Figure 2. Effect of independent variables (A) LSR and extraction time, (B) LSR and ethanol concentration, and (C) extraction time and ethanol concentration on the total flavonoid content value.

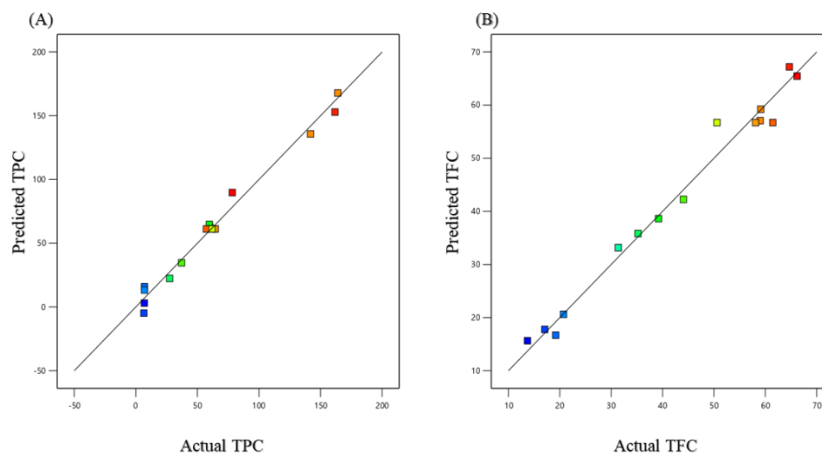


Figure 3. Comparison of predicted and actual levels of (A) total phenolics and (B) total flavonoids.

3.2 Validation of model

A summary of the model parameters and responses is presented in Table 2. The TPC and TFC assessments were evaluated with a quadratic model. The impact of the factors on the replies was assessed using ANOVA, with the summary results presented in Table 3. For both responses, the ANOVA table shows that the quadratic model produced satisfactory results. The R^2 figures for TPC and TFC values were 0.9850 and 0.9818,

respectively. This indicates that the quadratic model can explain 98% of the variability in predicting TPC and TFC values.

The precision model's output indicates that the R² and adjusted R² values of the quadratic equation model exceed 0.7684 and 0.8806 for TPC and TFC, respectively. This signifies that over 76.84% and 88.06% of the total variables in the findings may be ascribed to the research factors examined. These results are sufficiently elevated to validate the importance of the employed model. The model F values for TPC and TFC were 36.43 and 29.96, respectively, demonstrating that the model was significant (p 0.0005 and 0.0008) for both responses. ANOVA was utilized to assess the impact of the independent variables on both outcomes. The P values (Table 3) enabled the assessment of the significance level for each factor. This signifies that the model is sufficient to characterize the response values affected by the independent variables. The p-value for the LSR factor was <0.0001 for both responses, while the p-values for extraction time and ethanol concentration exceeded 0.05, indicating that not all independent variables significantly influenced the response; only LSR exhibited a significant effect on the response. This demonstrates a strong model adequacy in elucidating the influence of variable parameters, specifically ethanol concentration (%), liquid-solid ratio (ml/g), and extraction time (minutes) on the TPC and TFC assessments. The model's lack of fit is not substantial, suggesting that the predictions derived from the data have been calibrated and are applicable.

Table 3. ANOVA analysis for TPC and TFC responses

Source of Variation	Koefisien Regresi								
	TPC				TFC				
	Sum of Squares	d f	F-value	p-value	Sum of Squares	d f	F-value	p-value	
Model	40380,71	9	36,43	0,0005	4858,37	9	29,96	0,0008	*
A (%)	2464,61	1	20,01	0,0066	19,58	1	1,09	0,3449	
B (ml/g)	33607,98	1	272,85	< 0,0001	3969,64	1	220,34	< 0,0001	
C (min)	105,56	1	0,8570	0,3971	70,68	1	3,92	0,1045	
Residual	615,87	5			90,08	5			
Lack of Fit	589,75	3	15,06	0,0629	28,22	3	0,3041	0,8247	**
Pure Error	26,11	2			61,86	2			
Cor Total	40996,57	14			4948,45	14			
R ²	0,9850				0,9818				
R ² Adjusted	0,9579				0,9490				
R ² Predicted	0,7684				0,8806				
CV	17,68				9,95				
Adeq, Precision	19,0467				14,8728				

A: Ethanol Concentration; B: Liquid-solid Ratio; C: Extraction time

*: significant; **: not significant

3.3 Optimization of UAE factor variables

The desirability function approach was applied in this study using Design Expert. The independent variables were set in a range, with TPC and TFC responses optimised to

maximise. In this approach, individual desirability functions were calculated to combine all responses into one measure. This approach helps to predict the optimal level of the independent factors. The range of desirability is between 0 to 1.0, with values closer to 1.0 indicating the ability of the programme to produce products that increasingly meet expectations. However, the goal of optimisation is not to achieve a desirability value of 1.0, but rather to determine the best state that can satisfy all objective functions [31].

The optimum parameters established to enhance the TPC and TFC values are a LSR (mL/1 g) of 50 mL, an extraction duration of 26 minutes, too long an extraction time can have detrimental effects, as it can lead to the degradation of certain active compounds, especially those that are sensitive to temperature or pH [29]. And an ethanol concentration of 26.1238%, with a desirability value of 1. Under these extraction circumstances, TPC was measured at 152.259 GAE/g DE, while TFC was recorded at 68.5867 QE/g DE, both approximating the predicted values (Figure 4), with percentage errors of -7.7% and 3.5% , respectively, demonstrating excellent agreement with the predicted values. However, this is still acceptable because the % error value of the two responses is $< 10\%$. This verifies that the quadratic model employed is sufficiently robust for both replies[32].

A study by Turrini et al. reported that extraction using Ultrasonic-Assisted Extraction (UAE) resulted in higher polyphenol content (38–40 mg gallic acid/g dry matter) and flavonoid content (0.11–0.13 mg quercetin/g dry matter) compared to conventional soaking methods [33]. Our findings are consistent with these results, as UAE-treated lavender extracts showed increased TPC and TFC. This further reinforces the potential of UAE in enhancing the extraction of bioactive compounds from lavender.

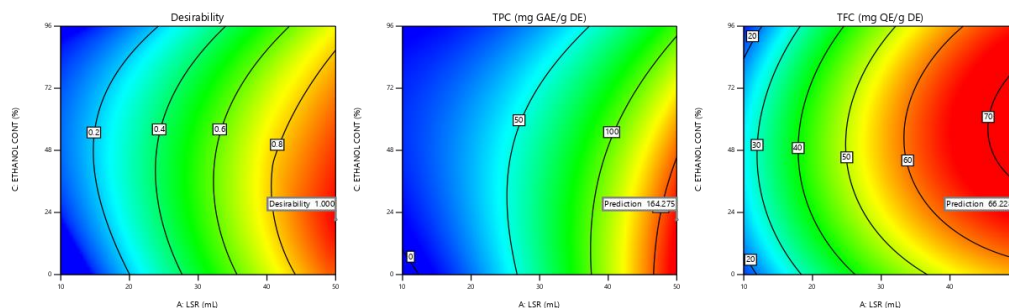


Figure 4. Contour plot of optimal condition of lavender extract

4. CONCLUSION

As the liquid-to-solid ratio (LSR) increases, the total phenolic content (TPC) and total flavonoid content (TFC) also increase. Similarly, higher ethanol concentrations and extended extraction times contribute to elevated TPC and TFC values, although an optimal point is observed. The optimization results demonstrate that the applied model is both robust and reliable. The ideal extraction parameters were 26.1238% ethanol concentration, a liquid-to-solid ratio of 50 mL/g simplicia, and an extraction duration of 26 minutes. Under these conditions, the TPC reached 152.259 mg GAE/g DE, while the TFC was 68.5867 mg QE/g DE.

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