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Optimization of Extraction Parameters for Phenolics and Flavonoids from Peony (*Paeonia lactiflora)* Flowers Using Ultrasound-Assisted Extraction

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Abstract
Peony (*Paeonia lactiflora*) flowers, celebrated for their aesthetic and bioactive attributes, possess potential as natural antioxidant sources owing to their elevated phenolic and flavonoid concentrations. This study employed ultrasound-assisted extraction (UAE) and response surface methodology (RSM) to optimize the extraction parameters for phenolic and flavonoid compounds. The Box-Behnken Design using method Ultrasoud Assisted Extraction determined the optimal extraction parameters of Paeonia lactiflora flowers to be 49% ethanol concentration, a liquid-to-solid ratio of 50 mL/g, and an extraction time of 22 minutes. The parameters yielded a total phenolic content (TPC) of 205.463 mg GAE/g DW and a total flavonoid content (TFC) of 95.465 mg QE/g DW. The results underscore the significance of the liquid-to-solid ratio as a critical factor in extraction efficiency, while ethanol concentration and extraction duration exhibited considerable interactive effects. The findings confirm the efficacy of UAE as a sustainable and efficient technique for extracting bioactive components from Paeonia lactiflora, indicating its potential use in pharmaceuticals and nutraceuticals. Future research should explore the antioxidant activity and IC50 values of these extracts for expanded therapeutic use.

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INTRODUCTION

Peony (*Paeonia lactiflora*), a flower with widespread ornamental appeal, originated in China and has since been cultivated globally in regions such as Europe and America (Kamenetsky-Goldstein & Yu, 2022). In addition to their visual appeal, flowers are rich in bioactive chemicals including flavonoids and phenolics, which have antioxidant effects and could be used in food, cosmetics, and medicines (Moreira et al., 2018).

Phenolic compounds are established as aromatic substances containing one or more hydroxyl groups, or their esters, methyl esters, and glycosides, characterized by the presence of at least one aromatic ring in their structure (Mahardani & Yuanita, 2021). These molecules are frequently glycosides, including mono-, di-, and tri-glycosides, in which glucose units are connected to the aryl ring via a hydroxyl group (Hidayah & Anggarani, 2022). These chemicals are thought to possess antioxidant properties in consumable plants. Researchers typically categorize them into two primary classes based on their bioactivity and potency: hydroxycinnamic acids and hydroxybenzoic acids (Kandylis, 2022). Similarly, flavonoids, secondary metabolites abundant in Paeonia lactiflora, exhibit a diverse range of bioactivities, including free-radical scavenging capabilities, which are essential for cellular protection against oxidative stress (Arifin & Ibrahim, 2018). Study by (Čutović et al., 2022) confirms the peony flower *(Paeonia lactiflora)* as a source of indigenous antioxidants and can be extracted

through various extraction techniques and solvents (Fibonacci & Hulyadi, 2018; Susiloningrum & Sari, 2023)

While conventional extraction techniques have been employed for obtaining phenolic and flavonoid compounds, these methods often face challenges such as high solvent consumption, extended processing times, and potential degradation of bioactive components (Bayani, Muhali, et al., 2024; Kusnadi et al., 2019). Modern advancements in extraction technologies, such as ultrasound-assisted extraction (UAE), offer a promising alternative (Shen et al., 2023). It enables the extraction of a greater quantity of secondary metabolites from diverse plant sources (Mahardani & Yuanita, 2021). It operates by generating appropriate cavitation effects on plant cell walls and membranes by ultrasonic waves of a specific frequency (Bayani, Rosmayanti, et al., 2024). Furthermore, it increases solvent uptake into cell membranes and mass transfer from plant tissues into the solvent (Bayani et al., 2023; Jihan Hana Fauziah et al., 2022)

Based on that background, research was conducted on the Optimization of Extraction Parameters for Phenolics and Flavonoids from Peony (Paeonia lactiflora) Flowers Using Ultrasound-Assisted Extraction. The findings of this study should provide scientific evidence and information that the bioactive chemicals found in peony flowers (Peonia lactiflora) have the ability to act as natural antioxidants and have other health-promoting properties. This research introduces a new approach for Paeonia lactiflora flower phenolic and flavonoid compound extraction through the combination of Box-Behnken Design and response surface methodology together with ultrasound-assisted extraction (UAE). This research developed a scientific extraction model that employs high accuracy to maximize the extraction yield of bioactive compounds. The research shows that UAE delivers effective and sustainable extraction methods for obtaining natural antioxidants that enable their use in pharmaceutical and nutraceutical sectors.

METHOD

Materials and Tools

The materials used in this study include Peonia lactiflora flower from Cirebon west java (elif tea and tisane), the chemicals and reagents used in this study include, “distilled water (Rofa Laboratory), gallic acid (Merck), quarcetin (Merck), 2,2-Diphenyl-1-picrylhydrazyl (Sigma Aldrich), methanol p.a (Merck), phenol folin-ciocalteu (Merck), $AlCl_3$(Merck).” The tools used in this study include a sonicator bath (EECOO, China), UV-Visible spectrophotometer (Shimadzu, Kyoto, Japan), and micropipette (Socorex, Switzerland).

Ultrasound-assisted Extraction

The extraction method used is the UAE (Ultrasound-Assisted Extraction) nonconventional extraction method following the method established by (Cheila et al., 2020) with modifications. The powder of peony flower *(Peonia lactiflora)* that has been mashed is weighed as much as 1 gram and then put into a 100 ml bottle, solvents with different ethanol concentrations and comparisons, and then covered with aluminum foil. After that, put the bottle into a sonicator bath with a temperature of 50^o with different extraction times, then filter the extract using a filter cloth and then put the liquid extract into a centrifuge tube, then put it into centrifugation at 4500 rpm for 5 minutes (Zhu et al., 2024). Analysis of Total Phenolic Content and Total Flavonoid Content was performed by placing the centrifuged products into microtubes (Chen & Wei, 2017). See Table 1 for a breakdown of the independent factors.

Table 1. Design of Experiment for Optimization of Extraction Process Peony flower

Independent Variables	Level		
	-1	0	+1
EtOH (%)	0	48	96
LSR (ml/g)	10	30	50
Extraction Time (minutes)	5	17.5	30
Dependent Variables	**Constraints**		
TPC (mg GAE/g DW)	Maximaze		
TFC (mg QE/g DW)	Maximaze		

Determination of total phenolic content (TPC)

The total phenolic content of peony flower extract *(Peonia lactiflora)* was assessed using the Folin-Ciocalteu method, with certain modifications based on the procedure proposed by (Akmal et al., 2024). An experiment utilizing Folin-Ciocalteu reagent in conjunction with a 7.5% Na_2CO_3 solution was performed on the sample to ascertain its total phenolic content. The absorbance at 765 nm was measured using a Kyoto, Japan-based Shimadzu UV1780 spectrophotometer after 45 minutes of incubation in a dark room temperature environment. The standard used to create the calibration curves was gallic acid, with concentrations ranging from 10 to 50 µg/ml (Noviyanty et al., 2019). The gallic acid content was determined using the absorbance equation. The absorbance data were then used to compute milligrams of gallic acid equivalent per gram of extract (mg GAE/g) (Widyasanti et al., 2018).

Determination of total flavonoid content (TFC)

The $AlCl_3$ (aluminum chloride) method was used to determine the total flavonoid content of peony flower extract (Peonia lactiflora). With the exception of measuring the absorbance at 453 nm using a UV-vis spectrophotometer (Shimadzu UV1780, Kyoto, Japan), this method followed the techniques indicated in a prior work by (Azizah et al., 2014). Just before this, 100 µl of 10% $AlCl_3$ was shaken with 0.5 ml of sample (500 µg/ml). This was followed by the addition of 100 µl of 1M CH_3COONa reagent, followed by another shaking of the mixture. Thereafter, it was allowed to incubate at room temperature for half an hour (Insanu et al., 2017). The concentration of quarcetin was expressed in milligrams per gram and connected to absorbance in order to create the calibration curve. The concentrations used for the experiment varied between 10 and 50 μg/ml (Rahmayani et al., 2013). next, the average concentration (μg/ml) of the sample was used to calculate its average absorbance. The amount of flavonoids in the extract was then measured and converted to milligrams of quarcetin equivalent per gram (mgQE/g).

Response Surface Experimental Design

Using Box-Behnken Design (BBD) for process optimization in the UAE, the study's authors identified the optimal parameters for peony flower extraction using Response Surface Methodology (RSM) (Diantoro et al., 2022). With the help of Design-Expert 13.0, the experimental data was formulated using the Box-Behnken design (BBD) method. We used a three-level design with three separate variable. The independent variables' ranges and values are defined in Table 1.

The investigators in this study repeated each measurement three times. The results of the TPC and TFC were statistically evaluated using the design expert program that is used to analyze RSM data. The effect sizes of the independent variables on the responses (TPC and TFC) were determined using analysis of variance (ANOVA). These effects were found to be linear, quadratic, and interaction effects. Statistical criteria such as coefficient of variation (CV),

adjusted coefficient of determination (R2), and adjusted R2 were utilized to assess the accuracy and adequacy of the models. The results were deemed significant at 95% ($p < 0.05$) and 99% ($p < 0.01$) (Almusallam et al., 2021).

RESULTS AND DISCUSSION

Extraction and optimization of phenolic compounds (TPC) and flavonoid compounds (TFC) from the peony flowers

Critical parameters in the extraction of phenolic chemicals using the UAE method include ethanol concentration, solid-liquid ratio, and extraction duration; these, in turn, affect the extraction of peony flowers (Akmal et al., 2024). This research looked at how total phenolic content (TPC) changed when different amounts of ethanol (A; 0-96%), durations of extraction (B; 5-30 min), and solid-liquid ratios (C; 10-50 ml) were used. Throughout the duration of the extraction, a steady temperature of 50°C was maintained. Table 2 displays the TPC and TFC values that were obtained from the extraction method. From 9.16 to 205.69 mg GAE/g DW, the peony flower extracts showed a total phenolic content (TPC), and from 27.06 to 88.52 mg QE/g DW, the total flavonoid content (TFC). For the purpose of estimating pure error, this BBD research design included fifteen experiments with three center point replicates (Azharini et al., 2022). This method optimizes each experimental response by making it easier to calculate intermediate responses and by allowing evaluation of system performance at each experimental point within the research range (Baek et al., 2024). Steps in the optimization process include checking the model's validity, fitting experimental data to the response function to estimate coefficients, evaluating the response of statistically determined combinations, and making predictions about the response based on the fitted model (Gündüz et al., 2023).

Table 2. Box Behnken design of three variables with their observed responses of peony flower extraction

Run	Ethanol (A) [%]	LSR (B) [ml/g]	Time (C) [min]	TPC [mg GAE/g DW]	TFC [mg QE/g DW]
1	48	30	17,5	77,68 ± 0,14	132,34 ± 0,14
2	48	30	17,5	77,18 ± 0,10	139,92 ± 0,11
3	96	30	5	75,82 ± 0,06	48,39 ± 0,04
4	0	10	17,5	9,17 ± 0,00	27,06 ± 0,94
5	48	30	17,5	76,35 ± 0,14	149,78 ± 0,19
6	0	50	17,5	204,41 ± 0,20	112,05 ± 0,20
7	0	30	30	75,06 ± 0,03	97,47 ± 0,82
8	48	50	5	195,90 ± 0,29	53,16 ± 0,00
9	48	50	30	205,69 ± 0,19	88,53 ± 0,00
10	48	10	5	9,52 ± 0,03	27,49 ± 0,40
11	48	10	30	9,35 ± 0,02	27,72 ± 0,00
12	0	30	5	74,43 ± 0,11	48,68 ± 0,18
13	96	10	17,5	9,26 ± 0,03	25,09 ± 0,32
14	96	50	17,5	200,45 ± 0,12	99,11 ± 0,00
15	96	30	30	79,32 ± 0,04	122,65 ± 0,07

* Each response is the average of triplicate with standard error

TPC: $(-1{,}821 + 0{,}0197_A - 0{,}037_B + 0{,}354_C + 0{,}0011_{AB} - 0{,}0010_{AC} + 0{,}0099_{BC} - 0{,}000045_{A^2} - 0{,}005184_{B^2} + 0{,}0721_{C^2})$

TFC: $(-127{,}96304 + 0{,}8589_A + 8{,}75721_B + 8{,}92562_C + 0{,}010611_{AB} - 0{,}002858_{AC} + 0{,}035137_{BC} - 0{,}009718_{A^2} - 0{,}249547_{B^2} - 0{,}131152_{C^2})$

Table 3 shows the outcomes of an analysis of variance (ANOVA) that was conducted to determine the effects of various treatment factors on TPC and TFC. The TPC and TFC values obtained from the peony flower demonstrated statistical significance ($p < 0.01$) based on the quadratic models that were built. The findings demonstrated that the samples were not significantly out of sync with one another ($p > 0.05$). The peony flower's TPC and TFC values were significantly affected by the linear terms of the Liquid Solid Ratio (C) ($p < 0.01$). Furthermore, there is no statistical significance ($p > 0.05$) for either the ethanol concentration (A) or the extraction length (B)(Andres et al., 2020).

R2 and adj-R2, the regression coefficients for the model fitted to the peony flower's TPC and TFC values, were close to unity. The outcomes show that the expected and actual values are identical. The reliability and accuracy of the experimental results are further supported by the small values of the coefficient of variation (CV). Results show that the suggested models work for estimating and optimizing peony flower phenolic and flavonoid component extraction (Fadimu et al., 2020).

Table 3. The impact of linear, quadratic, and interaction terms for TPC and TFC in peony flower samples is displayed in an ANOVA table.

Source	Koefisien Regresi							
	TPC				TFC			
	Sum of Square	df	F-value	P-value	Sum of Square	df	F-value	P-value
Model	77129,27	9	2421,68	<0,0001***	26830,68	9	7,59	0,0190
A (%)	0,3955	1	0,1118	0,7517^{ns}	12,42	1	0,0316	0,8658
B (minute)	23,64	1	6,68	0,0492^{ns}	3146,21	1	8,01	0,0367
C (mL/g)	73948,73	1	20896,36	< 0,0001***	7532,14	1	19,17	0,0072**
AB	2,06	1	0,5813	0,4802	162,13	1	0,4127	0,5489
AC	4,10	1	1,16	0,3308	30,12	1	0,0767	0,7929
BC	24,82	1	7,01	0,0455	308,64	1	0,7857	0,4160
A^2	0,0404	1	0,0114	0,9191	1850,86	1	4,71	0,0821
B^2	2,42	1	0,6845	0,4457	5613,60	1	14,29	0,0129
C^2	3074,85	1	868,89	<0,0001	10161,68	1	25,87	0,0038
Residual	17,69	5			1964,16	5		
Lack of Fit	16,80	3	12,54	0,0747	1811,29	3	7,90	0,1144
Pure Error	0,8930	2			152,87	2		
Cor Total	77146,97	14			28794,85	14		
R^2	0,9998				0,9318			
Adj-R2	0,9994				0,8090			
C.V%	2,05				24,79			

A: EtOH; B: Time; C: LSR (Liquid Solid Rasio).

***Significant($p < 0.001$); ** Significant ($p < 0.01$); * Significant ($p < 0.01$); Not Significant ($p>0.05$).

Effect of extraction variables on the TPC of peony flower extract

The results of the TPC experiments are displayed in Table 2. The range of acceptable results was 9.16–205.69 mg GAE/g DW. The highest yield was achieved with an ethanol concentration of 48%, a liquid-to-solid ratio of 50 mL/g, and an extraction period of 30 minutes as optimal conditions. The lowest yield was obtained by extracting the compound for 17.5 minutes at a liquid-to-solid ratio of 30 mL/g with no ethanol concentration. When the proportions of LSR and ethanol were considerably increased, the TPC value was found to be the greatest (Akmal et al., 2024).

Figure 1 shows three-dimensional response surface graphs that show the interaction between the peony flower extract's TPC and the independent variables of extraction time, ethanol concentration, and liquid-solid ratio. Scientific evidence suggests that a greater ratio results in increased total phenolic content (TPC) extraction from peony blooms when compared to a lower ratio and the same amount of time. The TPC concentration of each variable increases as the ethanol concentration and the liquid-solid ratio do. A substantial impact of extraction time on TPC values was not observed, however, when the results were analyzed in the context of the interaction between ethanol concentration and extraction length. This suggests that Total Phenolic Content (TPC) is not significantly enhanced by ethanol concentration or extraction duration (Paulo et al., 2022).

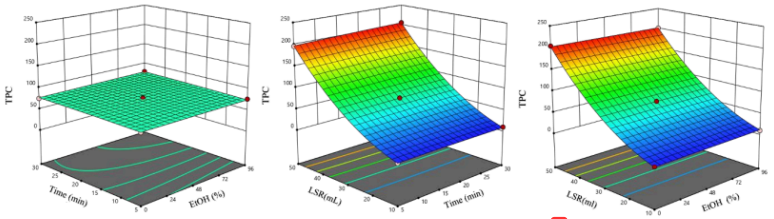

Figure 1. Effect of independent variables (A) LSR and extraction time, (B) LSR and ethanol concentration, and (C) extraction time and ethanol concentration on the TPC value.

This phenomenon can be ascribed to the saturation of TPC in the solvent or their degradation following prolonged extraction. The duration alone, alongside ethanol concentration, is inadequate to enhance the solubilization and diffusion of phenolics without considering optimal solvent ratios, as the increase in solvent polarity due to ethanol concentration necessitates the appropriate solvent ratio. Conversely, the solvent's extract ratio correlates with extraction time, demonstrating a significant rise in total phenolic content (TPC). A higher solvent ratio facilitates greater phenolic solubility, while extended extraction time enables deeper solvent penetration into the plant matrix. Similarly, enhancing the total phenolic content (TPC) derived from a specific solvent ratio with a designated ethanol concentration indicates an optimal solvent milieu that contains the appropriate quantity of total polar solute molecules inside a defined volume, conducive to effective phenolic extraction. These findings align with recent research emphasizing the significance of an optimum solvent ratio and ethanol concentration, namely within a 50–70% range, to attain effective phenolic recovery while maintaining compound stability (Şahin & Şamli, 2013).

Effect of extraction variables on the TFC of peony flower extract

Table 2 displays the experimental results for TFC. A range of 25.09 to 149.77 mg QE/g DW was reached in the results. At a concentration of 48% ethanol, an extraction duration of 17.5

minutes, and a liquid-to-solid ratio (LSR) of 30 mL/g, the peak was seen. At an ethanol concentration of 96%, an LSR of 10 mL/g, and an extraction time of 17.5 minutes, the lowest yield was observed. The peak TFC value was recorded at elevated ethanol concentration and LSR (Akmal et al., 2024).

The relationship among liquid-solid ratio (LSR), extraction length, ethanol concentration (EtOH%), and total flavonoid content (TFC) is clearly illustrated in a 3D perspective within the contour plot depicted in Fig 2. The correlation between leaf surface area (LSR) and time was delineated, indicating that a specific quantity of LSR is appropriate for total flavonoid content (TFC) (Wang et al., 2020). Although an initial rise in LSR enhances extraction efficiency, it ultimately reaches a threshold of diminishing returns. The interplay between time and ethanol content significantly affects the TFC. LSR and ethanol concentration influence each other, with yield TFC reaching its maximum at a specific threshold (Baek et al., 2024).

Several factors have been mentioned earlier, which clearly depict how much TFC can be extracted and can influence it. As for LSR, while a low one is made with a poor amount of solvent to dissolve the extracted flavonoid, an excessively high one causes the actual extracts to be diluted. The amount of faded time while doing the extraction is also an important factor, too short of an extraction time wouldn't help dissolve the flavonoids completely while risking ruining the constituent compounds at too long of an extraction time (Yang et al., 2024).

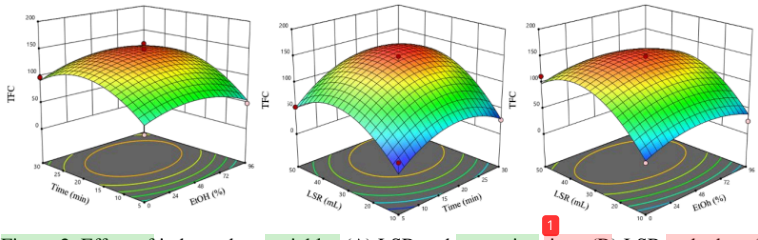

Figure 2. Effect of independent variables (A) LSR and extraction time, (B) LSR and ethanol concentration, and (C) extraction time and ethanol concentration on the TFC value

Optimization of the Extraction Parameters

The selected optimized parameters for employing the UAE extraction method follow (Athanasiadis et al., 2023) to obtain optimization of the extraction peony flower were EtOH 49%, Lsr 50 ml/g, and time 22 minutes. The optimal conditions were implemented to enhance the production of TPC and TFC. The optimal values achieved were TPC 205.463 mg GAE/g DW and TFC 95.4647 mg QE/g DW, corresponding to a generally desirable measure of 0.886 under the selected ideal conditions. These results indicate that the optimum conditions for peony flower extraction using the ultrasound-assisted extraction method have been well validated (Figure 3).

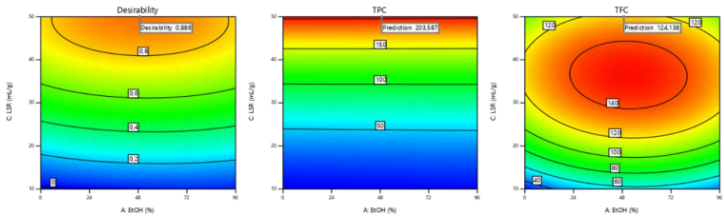

Figure 3. Desirability index plot for optimal extraction conditions of peony flowers

CONCLUSION

The process of extracting biologically active compounds, such as those with antioxidant-like phenolic and flavonoid compounds This study optimized the extraction of total phenolic content (TPC) and total flavonoid content (TFC) from Paeonia lactiflora flowers using ultrasound-assisted extraction (UAE) and response surface methodology (RSM) with Box-Behnken Design (BBD). While the liquid-to-solid ratio (LSR) was determined to be the most significant element ($p < 0.01$), there were interaction effects between the concentration of ethanol and the length of extraction. Under perfect conditions (49% ethanol, 50 mL/g LSR, and 22 minutes), a total of 205.463 mg GAE/g DW (TPC) and 95.465 mg QE/g DW (TFC) were produced. The validated model had an accuracy of 0.9998 for TPC and 0.9318 for TFC. Future research on extraction optimization can build on these findings, which show that UAE is an effective and environmentally safe way to extract bioactive chemicals with promising uses in medicines and nutraceuticals. Scientific and Industrial Relevance The use of response surface methodology (RSM) and Box-Behnken Design (BBD) enhances the precision of optimization studies in extraction research. These statistical tools help improve reproducibility and scalability, which are critical for industrial adoption

RECOMMENDATIONS

Further research on the antioxidant activity of peony flower extract in the form of determining the IC_{50} value.

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