



Development of a Simple and Rapid HPLC-UV Method for Ultrasound-assisted Deep Eutectic Solvent Extraction optimization of Ferulic Acid and Antioxidant Activity from *Ixora javanica* Flowers

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ABSTRACT

In this work, we developed an environmental friendly extraction method to enhance ferulic acid yields and antioxidant activity of *I. javanica* flowers using Ultrasound-assisted extraction (UAE) method and Deep Eutectic Solvents as green solvent. To optimize the extraction method, response surface method analysis using Box Behnken designs were conducted. The results showed that the optimum extraction conditions for ferulic acid yields, DPPH scavenging capacity, ABTS scavenging capacity and Ferric-Reducing Antioxidant Power featured an extraction time of 40 min, 25% water content, and solid-to-liquid ratio of 1/27 g/mL. In this study, a rapid and simple analytical method was also validated for the quantification of ferulic acid in *I. javanica* flower extract using LC-UV method. The developed method was carried out under following condition: isocratic mobile phase of acetonitrile/formic acid pH 2.55 (30:70), a flow rate of 0.8 ml/min, detection at 321 nm, and C-18 column (250 mm x 4.6 mm, 5 μm). The ferulic acid and antioxidant activity of the extract obtained from the developed were higher than ethanolic extract under same extraction condition. In summary, the results of this study can provide more effective and efficient extraction method by applying the green extraction principle and be recommended to provide new potential antioxidant raw material.

1. Introduction

Ferulic acid is a highly abundant compound in nature that has been widely applied in the pharmaceutical, food and cosmetic industries (Zduńska et al., 2018). Ferulic acid is well recognized for its activity as antioxidant and tyrosinase inhibitor (Liang et al. 2014). The separation of ferulic acid from natural products has been extensively studied for many years. Various extraction methods have been applied including conventional and non-conventional methods (Sun et al. 2006; Sun et al., 2008). However, most of these techniques are time consuming and usually involves organic and high-cost solvents. To avoid these limitations, a green non-conventional ultrasonic wave mediated techniques which is known as Ultrasound-assisted extraction (UAE) were recently

developed. In addition, the approaches of green extraction not only reducing the energy consumption but also the use of environmentally friendly solvents (Rutkowska et al., 2017; Chemat et al., 2012).

Deep Eutectic Solvents (DESs) is one of the popular green solvents that widely used in the green extraction application due to its advantages including cheap, easy preparation and less toxic. DESs are formed from combination of two or more compounds which can act as Hydrogen Bond Acceptor (HBA) and Hydrogen Bond Donor (HBD) with a certain ratio (García et al., 2015). Many previous studies showed that DESs are effective for metabolite compounds extraction from plants such as phenolics compound (). Moreover, several studies demonstrated that DESs can increase stability, and biological activity of natural and pharmaceutical compounds (Duan et al., 2016; Tang et al., 2016; Cao

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Table 1
Analytical conditions of HPLC for analysis of ferulic acid

Parameters	Conditions
Column	Inertsil™ ODS-3 (C18, 4.6 mm x 250 mm, 5µm)
Mobile phase	Acetonitrile/formic acid pH 2.55(30:70)
Flow rate	0.8 mL / min
Injection volume	20µL
UV detection	321 nm
Temperature column	25°C
Run time	10 menit

Table 2
The code of variable selected for the experimental study.

Variables	Code	Range and level (xi)		
		-1	0	1
Extraction Time (min)	X ₁	20	30	40
Water content (%)	X ₂	15	25	35
Solid-to-liquid ratio (g/mL)	X ₃	1/25	1/26	1/27

et al., 2017; Mustafa et al., 2021).

Ixora javanica (Rubiaceae) has been reported for its compounds and biological activities (Kharat et al., 2013). Its red flame color flowers are the most dominant plant part and are known to have many biological activities. *I. javanica* flower is known to have several biological activities such as anti-cancer, anti-inflammation, antioxidant and hepatoprotective effect. On the other hand, previous study reported that phenolic compounds of *I. javanica* extracts flowers responsible for tyrosinase inhibitor and antioxidant activity (Dontha et al., 2016).

Our previous study has investigated the antioxidant and tyrosinase inhibiting potency of *I. javanica* flowers extract. We also succeeded in developing the green extraction design to enhance flavonoids yields from *I. javanica* flowers using DESs as extraction solvent and UAE method (Oktaviyanti et al., 2019; Oktaviyanti et al., 2020). However, further investigation is still needed to optimize the specific compounds in *I. javanica* that are responsible to its activity. To the best our knowledge, research that simultaneous optimize its activity, especially

antioxidant activity and its active compounds, such as ferulic acid, has never been done before. Thus far, there is no research related to extraction optimization of ferulic acid and antioxidant activity from *I. javanica* using DESs and UAE has been reported.

In extraction optimization, a standardization process in order to identify and evaluate the ferulic acid in the extract using a validated analytical method is highly required (Kharat et al., 2013). To date, there is no validated analytical methods for quantification ferulic acid from *I. javanica* flowers extract have been reported in the literature elsewhere. So, in this study we also reported rapid, simple and validated analytical methods for quantification of ferulic acid using LC-UV method. This finding can provide support of quality control of *I. javanica* flower extract.

In brief, the main purpose of our study is to investigate the optimum condition for extraction of *I. javanica* flowers to provide high level of the ferulic acid and antioxidant activity which can be a new potential antioxidant raw material. At the same time, this study also provided an environmentally friendly extraction method for *I. javanica* flowers. Optimization many extraction variables such as extraction time, solid-to-liquid ratio, and water content was carried out using the response surface method (RSM). 2,2'-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azinbis (3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) scavenging capacities, and Ferric-Reducing Antioxidant Power (FRAP) were used as parameters of antioxidant activity which were optimized in this study.

2. Materials and Methods

2.1. Chemicals and Materials

The chemicals used in this study were choline chloride (Xi'an Rongsheng Biotechnology Co, Ltd, China); 1,2-propanediol, 1,3-propanediol, glycerol, ethylene glycol, polyethylene glycol, sorbitol, oxalic acid, lactic acid, glycolic acid, malic acid, and citric acid, TPTZ, FeCl₃·6H₂O, ABTS, (Merck, Germany); Ferulic acid, DPPH (Sigma Aldrich, USA).

In this work, the plant materials were collected from Tenggilis Mejoyo District, Surabaya, East Java, Indonesia and authenticated by

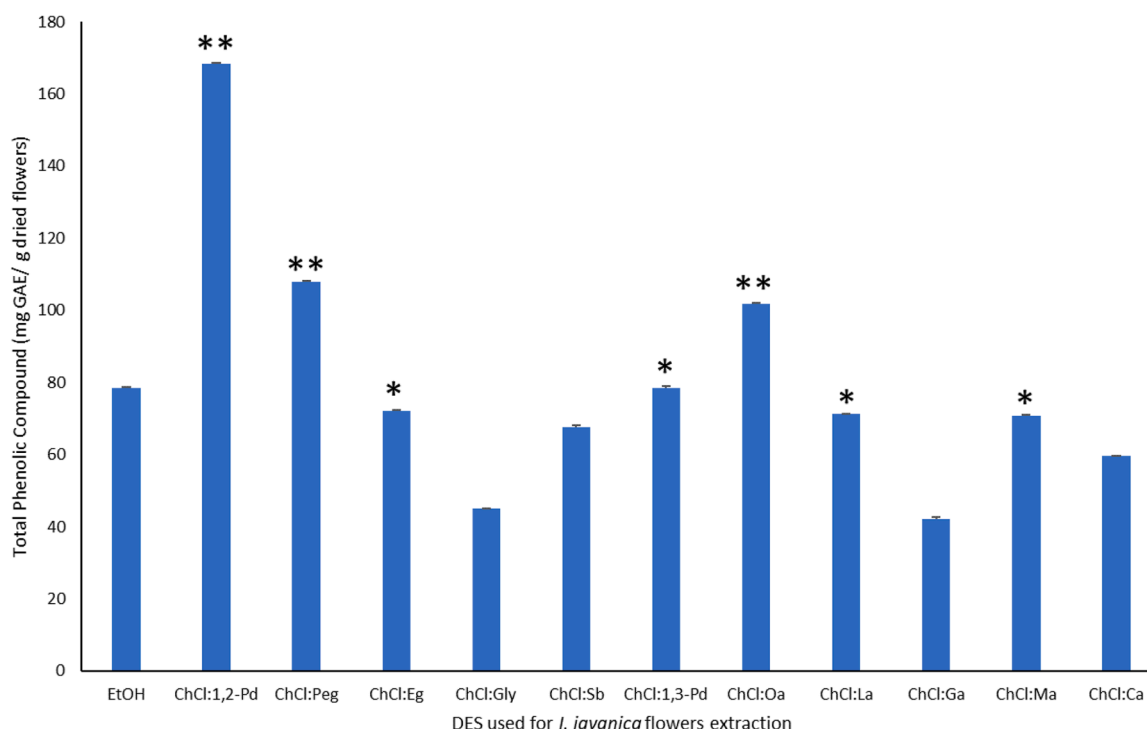
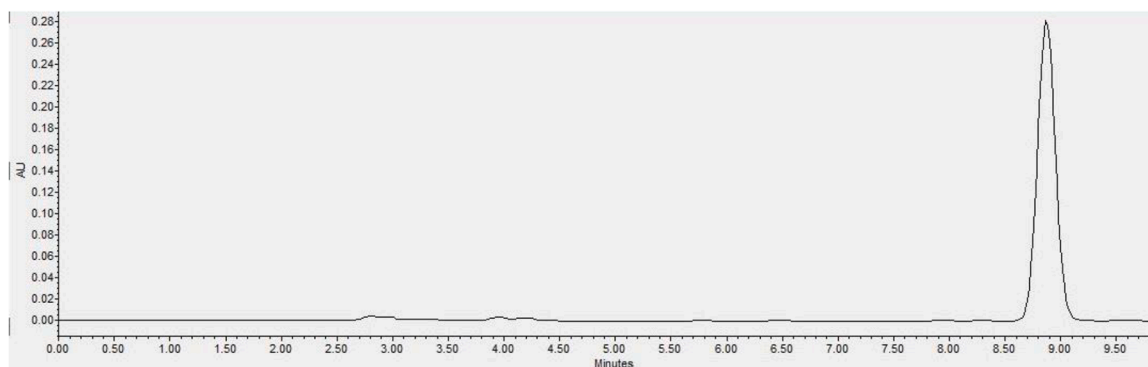
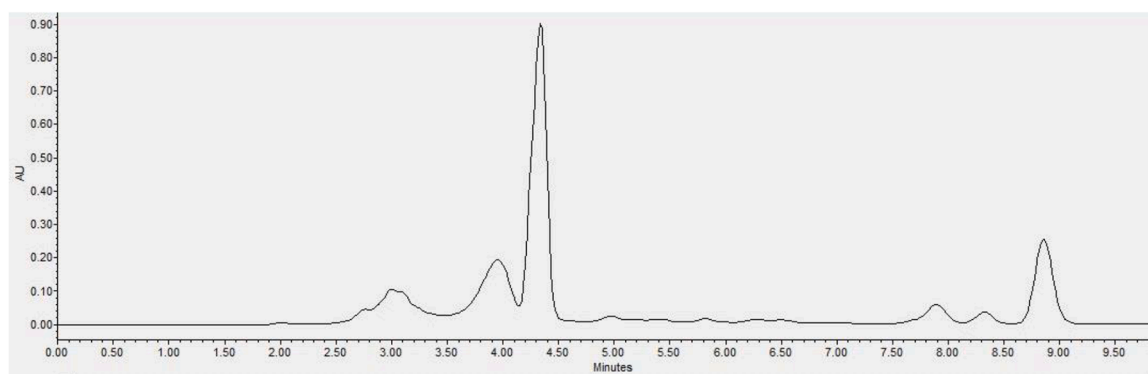


Fig. 1. Total phenolic yields from *I. javanica* flowers extract using different DES types. **p<0.05 compared with ethanol; *p>0.05 compared with ethanol



(a)



(b)

Fig. 2. Chromatogram of (a) standard and; (b) *I. javanica* flowers extract using DES

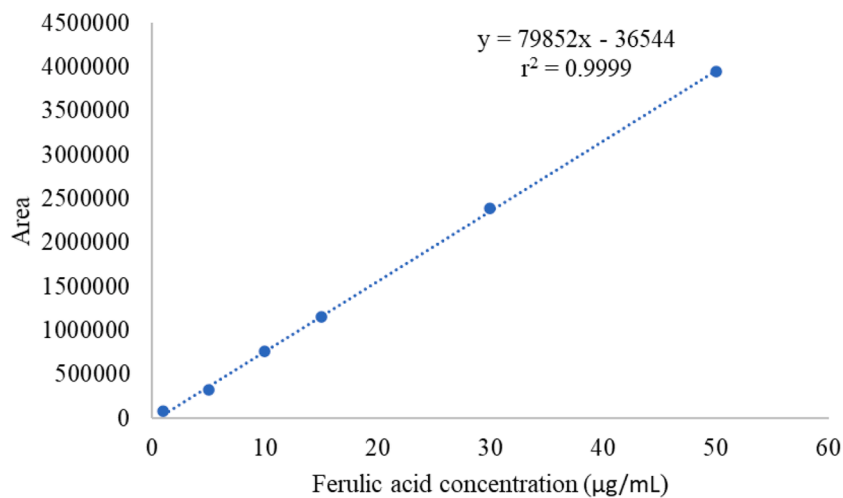


Fig. 3. Ferulic acid calibration curve

the Center for Traditional Medicine Information and Development, Faculty of Pharmacy, University of Surabaya.

2.2. Preparation of Deep Eutectic Solvents

In this study, about 11 choline chloride-based DESs were made by heat stirring HBA and HBD component at 50°C for 30 min constantly at certain molar ratios until a stable and homogeneous clear liquid mixture formed. The components used are Choline chloride (ChCl) as HBA combined with various HBD i.e 1,2-propanediol at molar ratio 1:1

(ChCl:1,2-Pd); polyethylene glycol at molar ratio 1:2 (ChCl:peg); ethylene glycol at molar ratio 1:2 (ChCl:Eg); glycerol at molar ratio 1:2 (ChCl:Gly); sorbitol at molar ratio 1:1 (ChCl:Sb); 1,3-propanediol at molar ratio 1:3 (ChCl:1,3-Pd); oxalyc acid at molar ratio 1:1 (ChCl:Oa); lactic acid at molar ratio 1:2 (ChCl:La); glycolic acid at molar ratio 1:1 (ChCl:Ga); malic acid at molar ratio 1:1 (ChCl:Ma); citric acid at molar ratio 1:1 (ChCl:Ca).

Table 3

Result of LC-UV analytical method intra-day and inter-day precision and accuracy

Intra-day (n=3)		
Concentration (µg/mL)	RSD (%)	Recovery (%)
5	1.19%	95.77%
10	1.29%	102.85%
15	1.93%	98.16%
Inter-day (n=3)		
Concentration (µg/mL)	RSD (%)	Recovery (%)
5	1.11%	96.38%
10	1.42%	98.37%
15	1.45%	98.93%

Table 4

Experimental values of experiment design

Run	Independent variable			Response			
	X ₁	X ₂	X ₃	Ferulic acid (mg/g dried flowers)	DPPH (%)	ABTS (%)	FRAP (AU)
1	-1	-1	0	0.3540	3.21	5.72	0.234
2	1	-1	0	3.4625	32.04	38.79	0.417
3	0	-1	-1	0.4697	16.88	18.56	0.201
4	-1	1	0	0.3825	7.72	7.58	0.125
5	-1	0	1	10.8344	47.72	55.14	0.756
6	-1	0	-1	6.5111	50.52	60.47	0.537
7	0	1	-1	0.4528	10.31	11.84	0.155
8	1	1	0	2.4728	24.41	28.88	0.305
9	0	0	0	7.8883	40.99	49.05	0.568
10	0	0	0	7.9749	40.37	49.28	0.564
11	0	-1	1	5.1113	3.91	5.56	0.494
12	1	0	1	12.9372	67.03	76.15	0.875
13	0	1	1	4.1088	9.88	9.93	0.354
14	1	0	-1	9.1859	78.27	88.40	0.649
15	0	0	0	7.8429	40.36	49.99	0.569

Table 5

Regression equation model

Response	Model equation*
Ferulic acid yields (mg/g dried flowers)	$Y = 7.90 + 1.25x_1 - 0.2476x_2 + 2.05x_3 - 0.2546x_1x_2 - 0.143x_1x_3 - 0.2464x_2x_3 + 0.5487x_1^2 - 6.78x_2^2 + 1.42x_3^2$
DPPH radical scavenging capacity (%)	$Y = 40.57 + 11.57x_1 - 0.4656x_2 - 3.43x_3 - 3.03x_1x_2 - 2.11x_1x_3 + 3.14x_2x_3 + 13.46x_1^2 - 37.18x_2^2 + 6.86x_3^2$
ABTS radical scavenging capacity (%)	$Y = 49.44 + 12.91x_1 - 1.30x_2 - 4.06x_3 - 2.94x_1x_2 - 1.73x_1x_3 + 2.77x_2x_3 + 14.68x_1^2 - 43.88x_2^2 + 5.91x_3^2$
FRAP (AU)	$Y = 49.44 + 12.91x_1 - 1.30x_2 - 4.06x_3 - 2.94x_1x_2 - 1.73x_1x_3 + 2.77x_2x_3 + 14.68x_1^2 - 43.88x_2^2 + 5.91x_3^2$

* Y: response variable; X₁: extraction time; X₂: water content (%); X₃: solid to liquid ratio (g/mL)

2.3. Ultrasound-assisted Extraction Procedure

The extraction process in this study was carried out by the UAE method according to previous study with very slight modification (Oktaviyanti et al., 2019). For DESs screening step, about 0.5 g dried flower powder was extracted with 10 ml extraction solvent (DESs or ethanol) at room temperature with ultrasonic frequency of 40 kHz. Residues were separated by centrifugation at 1500 rpm for 15 min and filtrate collected was adjusted until 10.0 ml final volume in volumetric flask. The same extraction procedures were carried out for *I. javanica* flowers optimization extraction where dried flower powder was extracted at specified extraction time, water content and solid-to-liquid ratio. All extraction procedures were conducted in triplicate.

Table 6

ANOVA for ferulic acid prediction model

Source	Sum of Squares	Degrees of freedom	Mean Square	F-value	p-value
Model	234.09	9	26.01	3439.63	< 0.0001
X ₁	12.44	1	12.44	1645.30	< 0.0001
X ₂	0.49	1	0.49	64.85	0.0005
X ₃	33.51	1	33.51	4430.98	< 0.0001
X ₁ X ₂	0.26	1	0.26	34.28	0.0021
X ₁ X ₃	0.08	1	0.08	10.82	0.0217
X ₂ X ₃	0.24	1	0.24	32.12	0.0024
X ₁ ²	1.11	1	1.11	147.03	< 0.0001
X ₂ ²	169.87	1	169.87	22464.27	< 0.0001
X ₃ ²	7.41	1	7.41	979.64	< 0.0001
Residual	0.04	5	0.0076		
Lack of Fit	0.03	3	0.0096	2.14	0.3347
Pure Error	0.01	2	0.0045		
Cor Total	234.12	14			

Table 7

ANOVA for DPPH radical scavenging capacity prediction model

Source	Sum of Squares	Degrees of freedom	Mean Square	F-value	p-value
Model	7628.18	9	847.58	3022.92	< 0.0001
X ₁	1071.38	1	1071.38	3821.13	< 0.0001
X ₂	1.73	1	1.73	6.17	0.0556
X ₃	94.12	1	94.12	335.68	< 0.0001
X ₁ X ₂	36.84	1	36.84	131.41	< 0.0001
X ₁ X ₃	17.81	1	17.81	63.51	0.0005
X ₂ X ₃	39.31	1	39.31	140.21	< 0.0001
X ₁ ²	668.53	1	668.53	2384.33	< 0.0001
X ₂ ²	5105.21	1	5105.21	18207.98	< 0.0001
X ₃ ²	173.55	1	173.55	618.97	< 0.0001
Residual	1.4	5	0.2804		
Lack of Fit	1.14	3	0.3805	2.92	0.2653
Pure Error	0.2605	2	0.1302		
Cor Total	7629.58	14			

2.4. Determination of total phenolic compounds

DES used in this study was selected using total phenolic compound yields. Each of extract was pipetted 0.1 mL then put into a volumetric flask. Water was added until it reached 10.0 mL of total volume and then shaken until homogeneous. Total phenolic levels from *I. javanica* flowers extract were analysis as the Total Phenolic Index (TPI) and the absorbances read by spectrophotometer (UV-1900, Shimadzu Corp, Kyoto) at a wavelength of 280 nm as which refers to the method of Aleixandre-Tudo et al. (2017) with slight modifications. The reference compound used for the phenolic compound was Gallic acid. Total phenolic level was expressed as mg GAE per g dried flowers (mg GAE/g dried flowers). All analyses were performed in triplicate.

Table 8
ANOVA for ABTS radical scavenging capacity prediction model

Source	Sum of Squares	Degrees of freedom	Mean Square	F-value	p-value
Model	10117.97	9	1124.22	614.97	< 0.0001
X ₁	1334.32	1	1334.32	729.89	< 0.0001
X ₂	13.53	1	13.53	7.4	0.0418
X ₃	131.99	1	131.99	72.2	0.0004
X ₁ X ₂	34.6	1	34.6	18.93	0.0074
X ₁ X ₃	11.98	1	11.98	6.55	0.0506
X ₂ X ₃	30.74	1	30.74	16.81	0.0094
X ₁ ²	796.11	1	796.11	435.49	< 0.0001
X ₂ ²	7110.55	1	7110.55	3889.59	< 0.0001
X ₃ ²	129.11	1	129.11	70.63	0.0004
Residual	9.14	5	1.83		
Lack of Fit	8.66	3	2.89	11.9	0.0785
Pure Error	0.4851	2	0.2425		
Cor Total	10127.12	14			

Table 9
ANOVA for FRAP prediction model

Source	Sum of Squares	Degrees of freedom	Mean Square	F-value	p-value
Model	0.6943	9	0.0771	147.150	< 0.0001
X ₁	0.0441	1	0.0441	84.130	0.0003
X ₂	0.0207	1	0.0207	39.5	0.0015
X ₃	0.1097	1	0.1097	209.34	< 0.0001
X ₁ X ₂	2.25E-06	1	2.25E-06	0.0043	0.9503
X ₁ X ₃	0	1	0	0.0234	0.8845
X ₂ X ₃	0.0022	1	0.0022	4.21	0.0953
X ₁ ²	0.0105	1	0.0105	19.97	0.0066
X ₂ ²	0.4523	1	0.4523	862.77	< 0.0001
X ₃ ²	0.0261	1	0.0261	49.7	0.0009
Residual	0.0026	5	0.0005		
Lack of Fit	0.0026	3	0.0009	124.15	0.080
Pure Error	0	2	7.00E-06		
Cor Total	0.6969	14			

2.5. LC-UV Validation Method for Ferulic Acid Quantification

Ferulic acid quantification in *I. javanica* flowers extracts were performed using LC-UV method. Previously, the method was validated for many parameters: specificity, linearity, sensitivity, accuracy and precision (ICH Guidelines). Analysis was performed using Waters 1525 HPLC system with UV-Vis detector employing isocratic system. Before used, the solvents were filtered through a 0.22 µm filter and degassed. Analytical conditions of HPLC for analysis of ferulic acid were shown at Table 1.

2.5.1. Specificity

The chromatograms profile of the standard solution and sample solution were compared. It was carried out to find out whether the method can discriminate targeted analyte with other constituents in the sample extract (Seo et al., 2016).

2.5.2. Linearity

The linearity was analyzed by calibration curves of six concentration of ferulic acid standard (1, 5, 10, 15, 30, and 50 µg/mL). Each standard concentration was analysis in triplicate. The linear regression analysis

and linear regression coefficients (r) were determined by intrapolating the standard concentration (x axis) and data peak area (y axis).

2.5.3. Sensitivity

LOD and LOQ were calculated using following equation (Eq. (1) and Eq. (2)):

$$LOD = \frac{SDR \times 3}{S} \quad (1)$$

$$LOQ = \frac{SDR \times 10}{S} \quad (2)$$

While SDR is the standard deviation of response; S is slope of the calibration curve.

2.5.4. Accuracy and precision

The accuracy was determined at three different concentration levels standard to the sample corresponding to 5, 10, and 15 µg/mL within same and different days, in triplicate. The intra-day and inter-day accuracy value is expressed in recovery percentage (% recovery) while the intra-day and inter-day precision in relative standard deviation (% RSD).

2.6. In Vitro Evaluation of Antioxidant Activity

2.6.1. Determination of DPPH Radical Scavenging Capacity

DPPH assay was performed of previous study with modification (Oktaviyanti et al., 2019). About 1.5 mL sample solution were mixed with 1.5 mL of 100 µg/mL DPPH solution. The mixture was incubated for 5 min and the absorbance was analyzed at 523 nm (A). The 50 µg/mL DPPH solution was also read for its absorbance (A₀). All procedures were performed in dark condition and room temperature, in triplicate. DPPH Radical Scavenging Capacity were calculated as percentage inhibition (% inhibition) using following Equation (Eq. (3)):

$$\% \text{ inhibition} = \frac{A_0 - A}{A_0} \quad (3)$$

2.6.2. Determination of ABTS Radical Scavenging Capacity

The ABTS radical scavenging capacity was analyzed using spectrophotometric method described by Proestos et al. (2013) with modification. The ABTS radical was prepared by mixing 28.4 mg ABTS and 14.0 mg K₂S₂O₈ in a volumetric flask and deionized water was added until total volume of 100.0 mL. The mixture was incubated in dark room for 12-16 h. A volume of 1.5 mL sample extract solution was added to 1.5 mL ABTS radical solution, and the mixture was kept at room temperature. The absorbance was measured at 730 nm after incubated for 5 min. The data of sample absorbance (A) and ABTS radical solution (A₀) were calculated as percentage inhibition (% inhibition) using Eq. (3). All analysis procedures were performed in triplicate.

2.6.3. Determination of Ferric-Reducing Antioxidant Power (FRAP)

Assay were performed as previously describe by Proestos et al (2013) with slight modification. Previously, 187 mg sodium acetate trihydrate was mixed with 16 ml acetic acid and added with 250 mL distilled water. Then, FRAP solution was made by mixing 25 mL of the mixture, 2.5 mL TPTZ solution (150 mg TPTZ in 50 mL of 40 mM HCl), and 2.5 mL FeCl₃.6H₂O solution (270 mg FeCl₃.6H₂O in 100 mL distilled water). The mixture then transferred to a volumetric flask and distilled water was added until 100.0 mL final volume. Each of extract solution and FRAP solution with same volume were mixed and incubated for 5 min. All the mixtures were analyzed using spectrophotometer UV-Vis at 600, 50 nm. All analysis was done in triplicate.

2.7. Experimental Design

The extraction variables were optimized using response surface

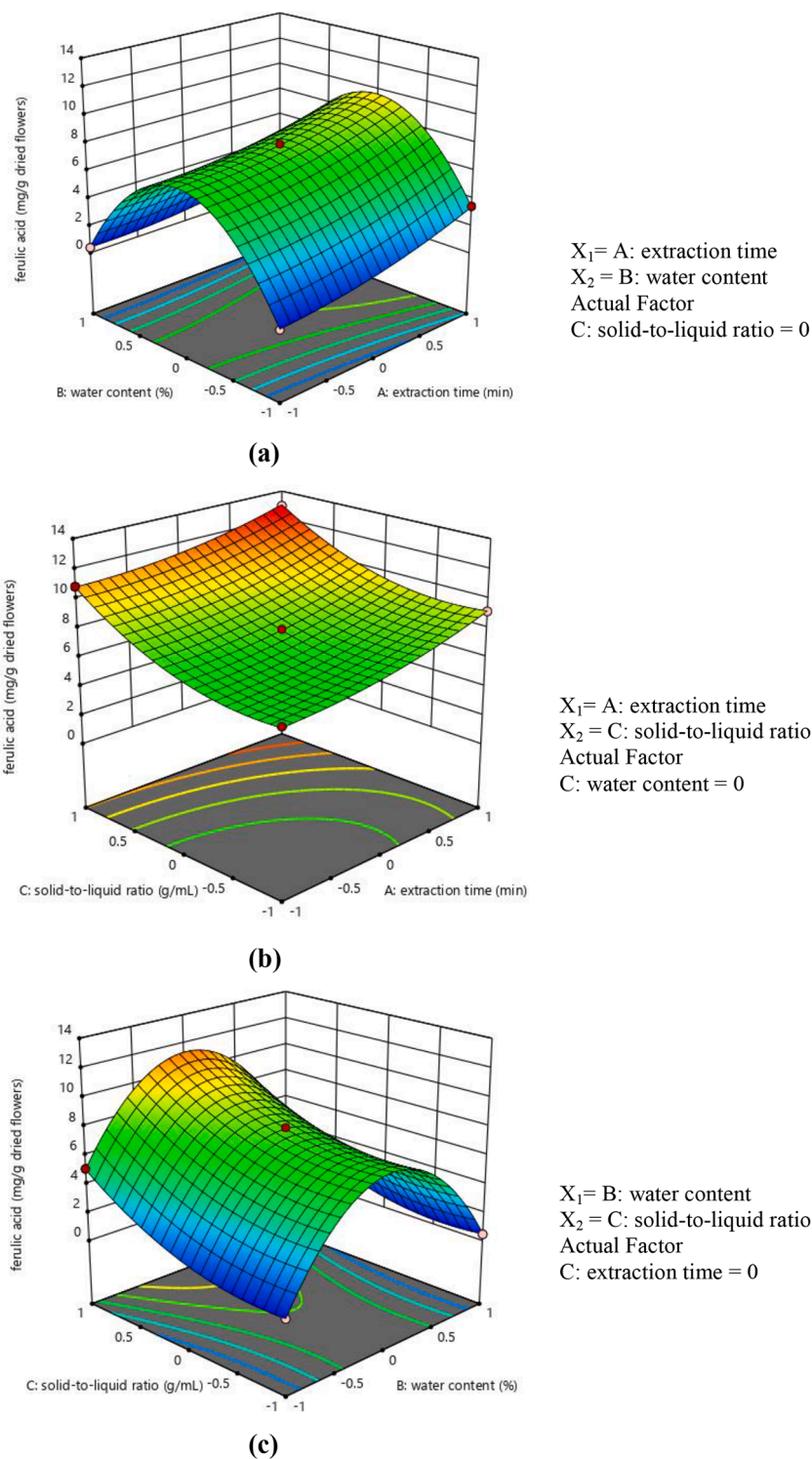


Fig. 4. 3D response surface graphs of ferulic acid yield versus (a) extraction time (x_1) and water content (x_2); (b) extraction time (x_1) and solid-to-liquid ratio (x_3); (c) water content (x_2) and solid-to-liquid ratio (x_3).

methodology (RSM) and Box Behnken Design (BBD) was chosen to predict the optimum extraction condition. In this study, three independent variables with three levels were determined based on our previous study (Oktaviyanti et al., 2020). The code of each levels of independent variable used for experimental study given in Table 2. A second-order polynomial model used to predict the optimum extraction condition according following equation (Eq. (4)):

$$Y = \beta_0 + \sum_{j=1}^3 \beta_j X_j + \sum_{j=1}^3 \beta_{jj} X_j^2 + \sum_{i=1}^2 \sum_{j=i+1}^3 \beta_{ij} X_i X_j \quad (4)$$

where Y is the response variable (ferulic acid yields, DPPH radical scavenging capacity, ABTS radical scavenging capacity, and Ferric-Reducing Antioxidant Power); β_0 is a constant and represents the intercept; β_j , β_{jj} , β_{ij} are the linear, squared and interaction coefficients, respectively (Jing et al., 2015).

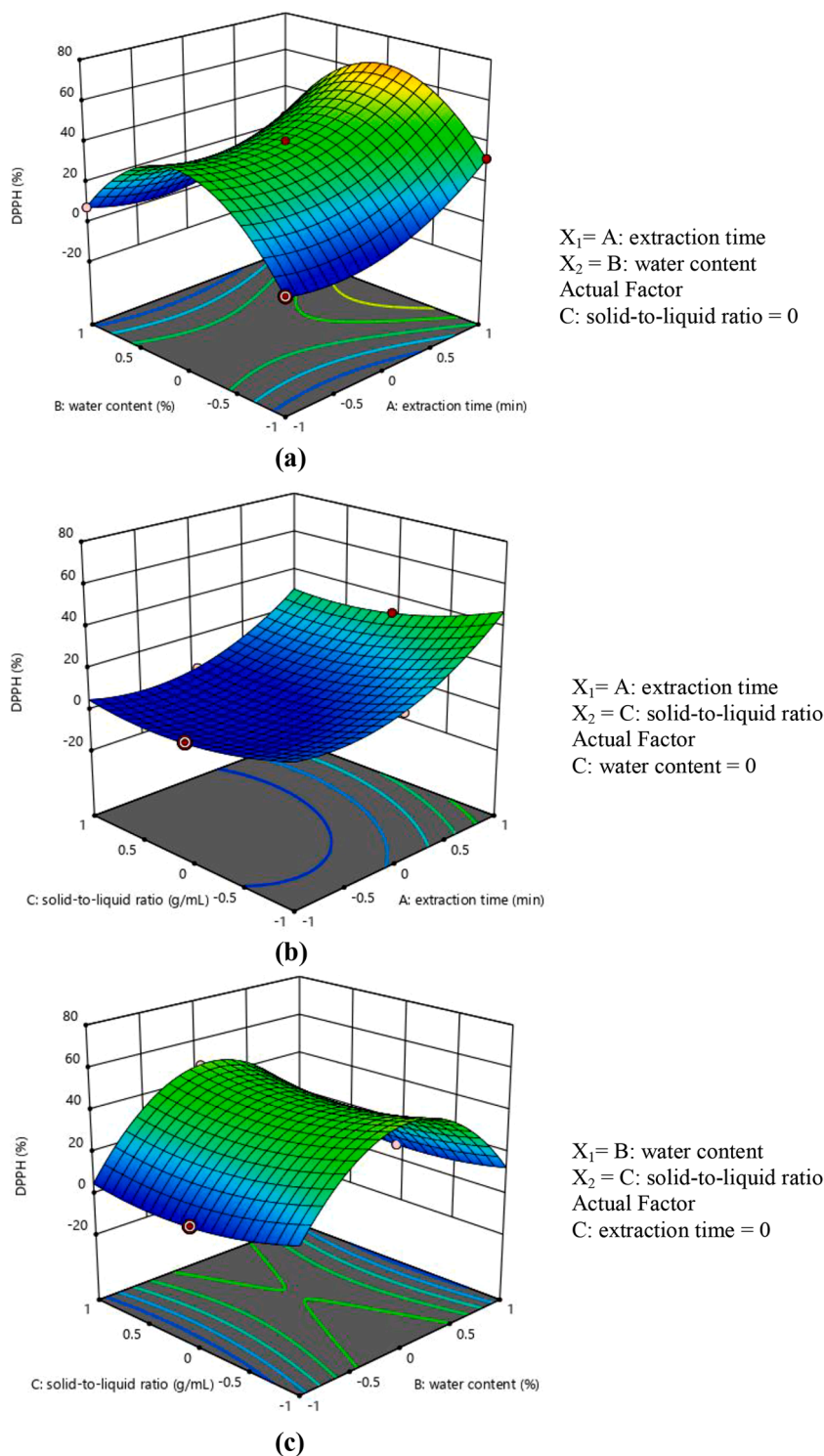


Fig. 5. 3D response surface graphs of DPPH radical scavenging capacity versus (a) extraction time (x_1) and water content (x_2); (b) extraction time (x_1) and solid-to-liquid ratio (x_3); (c) water content (x_2) and solid-to-liquid ratio (x_3).

2.8. Statistical Analysis

The data of total phenolic yields in this study were analyzed via one-way analysis of variance (ANOVA) test (significance level of $p < 0.05$) using SPSS software version 18 for Windows (IBM, New York, United States). Meanwhile, ferulic acid yields and antioxidant activity were processed using Design Expert software version 11, Stat-Ease Inc., Minneapolis, MN, USA.

3. Results and Discussion

3.1. Optimal DES for extraction

The parameter used for selecting optimal DES for *I. javanica* flowers extraction was total phenolic compound yields. Twelve different choline chloride-based DES were evaluated for extraction of total phenolics. The combination of choline chloride as HBA and 1,2-propanediol as HBD at molar ratio 1:1 showed the highest total phenolic compound yields

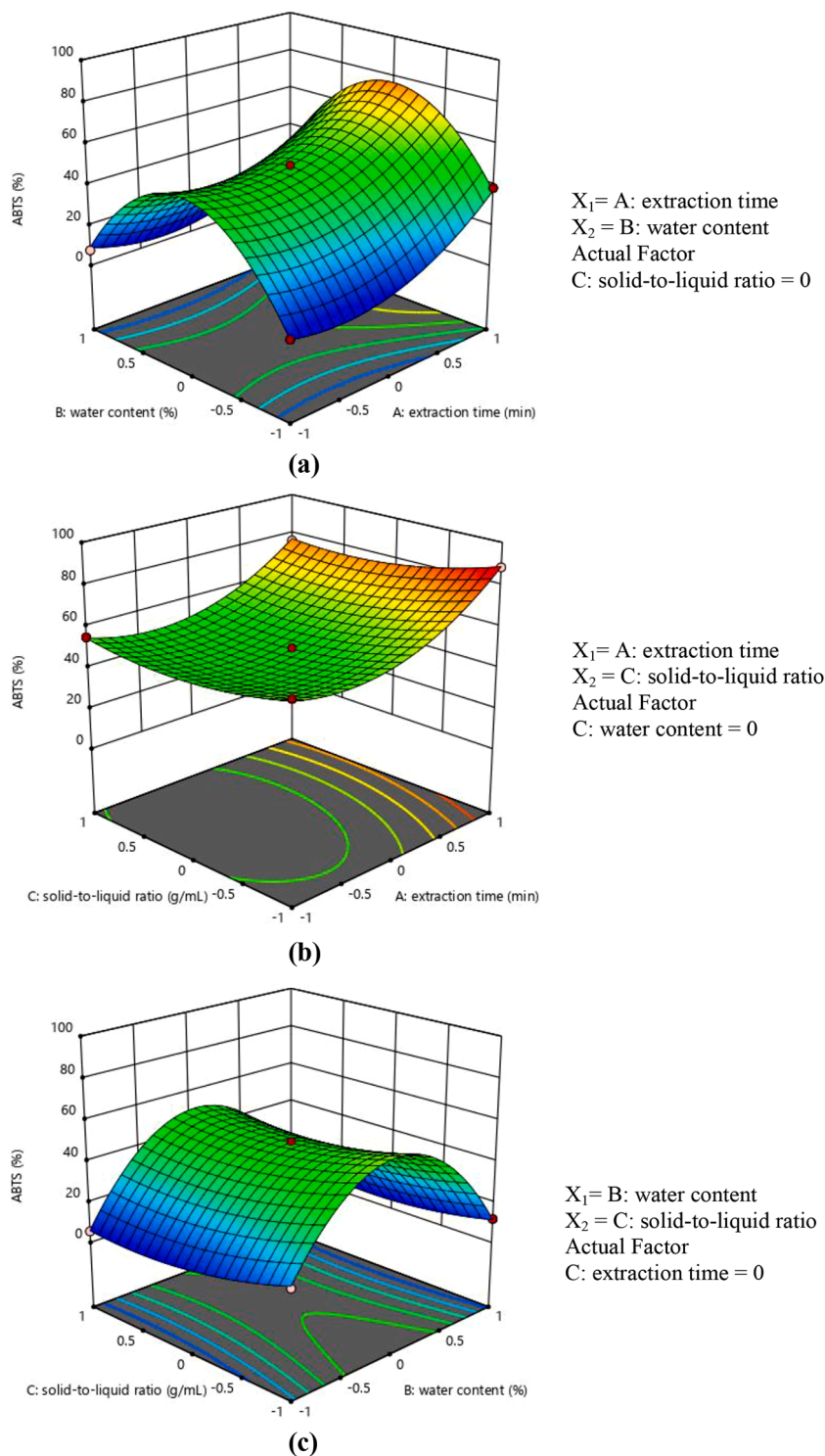


Fig. 6. 3D response surface graphs of ABTS radical scavenging capacity versus (a) extraction time (x_1) and water content (x_2); (b) extraction time (x_1) and solid-to-liquid ratio (x_3); (c) water content (x_2) and solid-to-liquid ratio (x_3).

(Fig. 1). We also compared the phenolic compound yields with that obtained for ethanolic extract and encouraging results were obtained. Three of among the DES used in this study showed higher capability in total phenolic compound extraction to ethanol ($p < 0.05$) and four DES showed insignificant extraction yields compared to ethanol ($p > 0.05$). This demonstrated that DES possible for replacement the use of conventional solvents in phenolic compound extraction, even better. Our previous studies also showed the same result for total flavonoid extraction using UAE method (Oktavianti et al., 2019).

3.2. The Optimal Chromatographic Condition for Ferulic Acid

We were performed an optimization of chromatographic condition in order to validate an efficient method for the quantification of ferulic acid. The mobile phase, separation method system (isocratic or gradient), flow rate, and wavelength were investigated to obtain the best separation condition. Detection wavelengths of ferulic acid were set at 321 nm according to its ultraviolet (UV) absorption maxima. This result is similar with the study conducted by Xie et al. (2007) where ferulic acid

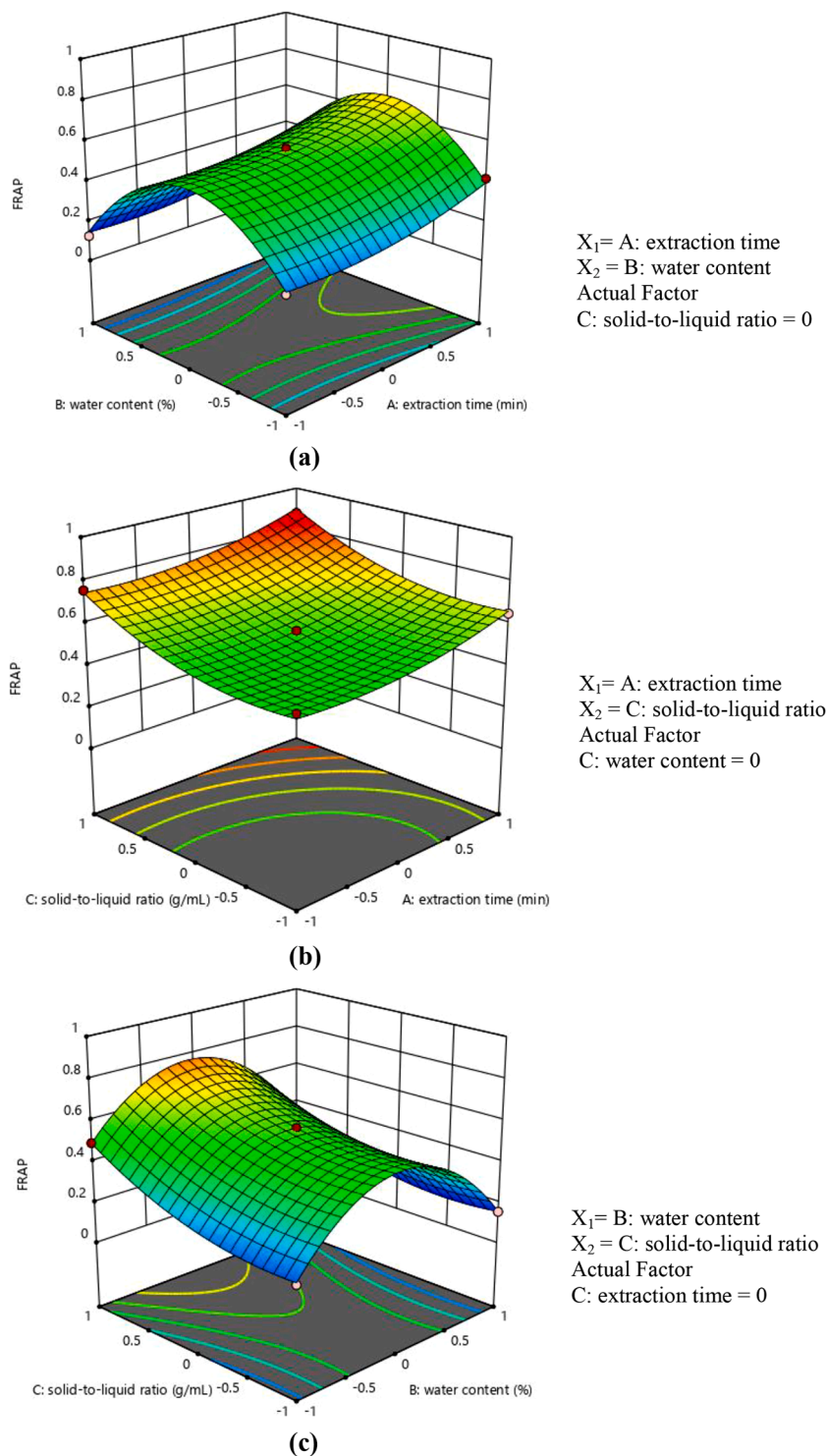


Fig. 7. 3D response surface graphs of FRAP versus (a) extraction time (x_1) and water content (x_2); (b) extraction time (x_1) and solid-to-liquid ratio (x_3); (c) water content (x_2) and solid-to-liquid ratio (x_3).

was analyzed at a wavelength of 320 nm. The mobile phase used in this study consists of Acetonitrile and formic acid pH 2.55 in ratio 30:70 v/v. In a previous study conducted by Kareparamban et al. (2013) also used an acidic mobile phase at pH 2.25 for the separation of ferulic acid. Theoretically, the separation procedure for phenolic compounds generally uses a mobile phase with a pH range of 2-2.5 to obtain a good separation (Sherma et al., 2003). Generally, mobile phase with a pH range of 2-2.5 used in phenolic compounds analysis and provide good separation (Sherma et al., 2003). In this study, ferulic acid was detected

at retention time 8.88 min with resolution (R_s) value of 2.03 and tailing factor (TF) of 0.95. Fig. 2 showed chromatographic profile of ferulic acid standard and sample extracts.

3.3. Method Validation for Ferulic Acid Determination

The specificity, linearity, sensitivity, accuracy and precision of ferulic acid quantification method using LC-UV were done. The ferulic acid calibration curves (Fig. 3) were linear within the concentration range of

Table 10
Experimental and predicted values of all response variables under optimal UAE condition

Response	DES-UAE extract Experimental* Value	Predicted Value	Ethanollic extract*
Ferulic acid yields (mg/g dried flowers)	12.937 ± 0.169	13.025	6.349 ± 0.282
DPPH radical scavenging capacity (%)	67.03 ± 0.288	66.92	42.66 ± 0.58
ABTS radical scavenging capacity (%)	76.15 ± 0.660	77.12	40.89 ± 0.59
FRAP (AU)	0.880 ± 0.012	0.898	0.27 ± 0.01

* Results are mean ± SD (n=3)

1–50 µg/mL and the linear equation was: $y = 79852x - 36544$. The analytical curve presented good linear regressions with coefficient determination 0.9999 ($r^2 > 0.99$) (Oliveira et al., 2019). The LOD and LOQ of ferulic acid in this present method was 1.3582 and 4.5272 µg/mL, respectively. Table 3 shows intra-day and inter-day precision of low (5 g/mL), medium (10 g/mL) and high-concentrations (15 g/mL) of ferulic acid standard addition.

All of the relative standard deviation (RSD) values were less than 2.5% (meet the requirement of the ICH guidelines). In addition, the recovery percentage of ferulic acid were in the range of 95.77–102.85%. This method is proven to provide good separation and faster analysis time of ferulic acid when compared to the previous study. Thus, it can be concluded that this developed method was exhibited a precise and accurate method for ferulic acid quantification.

3.4. The Optimal UAE Condition for Ferulic Acid and Antioxidant Activity

Independent variables for RSM selected based on our preliminary testing and previous study were extraction time (20–40 min), water content (15–35%), and solid to liquid ratio (1/27–1/25 g/mL) (Liang et al., 2014).

The response surface methodology with a Box Behnken design was conducted to determine the optimal UAE condition for ferulic acid and antioxidant activity. About 15-runs of the RSM experiment were performed to verify the predictive model of ferulic acid yields, DPPH radical scavenging capacity, ABTS radical scavenging capacity and FRAP. The results of all response can be seen in Table 4. In order to determine the relationship between the variables and response, all of the data from experimental study were then analyzed using Design Expert software to obtain a regression equation which is a model to predict each response (Table 5).

Furthermore, ANOVA was performed for evaluating the model quality of each response and the results are shown in Tables 6, 7, 8, and 9. The R^2 values of all models show that there is a great agreement between the experimental results and the predicted yield. The model can express variances of more than 99.79% ($R^2 = 0.9979$); 99.75% ($R^2 = 0.9975$); 98.62% ($R^2 = 0.9862$); and 94.01% ($R^2 = 0.9401$) for ferulic acid, DPPH, ABTS and FRAP, respectively. Table 6, 7, 8, and 9 also show that among variables have a significant effect on the responses (p -value < 0.05). Furthermore, the models show that the lack-of-fit was statistically-insignificant (p -value > 0.05), where p value 0.3347; 0.2653; 0.0785; and 0.080 for ferulic acid, DPPH, ABTS and FRAP, respectively. A good model must show insignificant lack-of-fit value which means that the failure of the model to represent the data is not significant, so the model is appropriate to predict the responses (Liang et al., 2014). Moreover, we investigated the interactive effect of variables on ferulic acid, DPPH, ABTS and FRAP. The results are represented as response surface plot on 3D surface graphs (Figs. 4, 5, 6, and 7) where a variable was held at zero level, while varying other two variables.

The UAE method has been known for its high extraction efficiency which is mediated by the cavitation phenomenon. Cavitation phenomenon generated by ultrasonic waves can cause cell membrane rupture without needing to increase the temperature (Ravanfar et al., 2018). In the cavitation process, ultrasonic waves trigger the formation, enlargement and rupture of microbubbles in the liquid medium. The mechanisms of the UAE method is related to the cavitation phenomenon that can increase the extraction efficiency, including phenolic compound extraction (Panda and Manickam, 2019). Several studies reported the effect of ultrasonic waves on the surface of plant cells include fragmentation, erosion, sonocapillary effects, sonoporation, local shear stress, and detexturation (Chemat et al., 2017). Ultrasound cavitation causes particles fragmentation resulting in a particle size reduction, thereby shorten the extraction time and increased extract recovery. Microbubble cavitation phenomenon can initiate an increasing of porosity and facilitate solvent penetration. In addition, cavitation is also able to increase the permeability of the cell membrane or also known as the sonoporation effect (Petigny et al., 2013; Xie et al., 2015; Rodríguez-pérez et al., 2015).

Thus, UAE is widely used in the green extraction application to reduce extraction time and energy consumption (Tiwari, 2015). Our result showed that ferulic acid and antioxidant activity were increase along increasing of extraction time. In the UAE method, the longer contact time between the solvent with sample and provided a greater opportunity for mass transfer. Several previous studies were found have similar trend with our result (Sun et al., 2008; Syakfanaya et al., 2019; Suhaimi et al., 2019).

The high viscosity is a common problem of DES that can interfere the extraction process. Several studies carried out the water addition to the DES mixture to solve DES viscosity problem (Cao et al., 2018; Makoś et al., 2020). Our results demonstrated that increasing water addition in DES resulted in higher extraction efficiency, which reached a maximum at water content of 25%. The water addition gave quadratic effect on ferulic acid yields and antioxidant activity. Furthermore, greater amount of water can affect the hydrogen bond formation and polarity of the DES (Sang et al., 2018). This can be seen from our results where the addition of water above 25% subsequently decreased extraction yields and activity.

Several studies carried out to determine the optimal solid-to-liquid ratio in extraction process (Ahmad et al., 2018; Xie et al., 2015; Agcam et al., 2017). In this study, lower value of solid-to-liquid ratio cause increased the extraction efficiency of ferulic acid and antioxidant activity. This may indicate the higher volume solvents used for extractions facilitate the mass transfer of bioactive compounds (Chong et al., 2015).

3.5. Verification of Response Surface Models

All experimental responses in this study including ferulic acid and antioxidant activity were used to predict the optimal extraction conditions from *I. javanica* flowers. The best UAE condition for *I. javanica* flowers obtained from the RSM software are extraction time of 40 min, 25% water content, and solid-to-liquid ratio of 1/27 g/mL.

Our finding shows that optimal value from experimental data corresponds to 99.32, 100.16, 98.74, and 98.00% of the predicted value for ferulic acid, DPPH, ABTS and FRAP respectively (Table 10). It is demonstrating that the model was suitable to predict the data.

Furthermore, ferulic acid yields and antioxidant activity of *I. javanica* flowers extract in optimal extraction condition compared to ethanolic extract are also shown at Table 10. In present study, ethanol was chosen as a comparison because it is a conventional organic solvent that widely used as an extracting solvent. Surprisingly, *I. javanica* flowers extract UAE using DES as extraction solvent showed higher ferulic acid and antioxidant activity than ethanolic extract under the same conditions.

4. Conclusion

An environmentally friendly extraction method has been successfully employed to enhance the ferulic acid yields and antioxidant activity of *I. javanica* flowers extract. A simple and validated analytical methods for quantification of ferulic acid in *I. javanica* flower extract using LC-UV method also succeeded to develop. The optimum extraction conditions suggested from this study were extraction time of 40 min, water content of 25%, and solid-to-liquid ratio of 1/27 g/mL. Thus, the use of DES (Choline chloride and 1,2-propanediol at molar ratio 1:1) and UAE method under our optimal extraction condition has been proven can be a promising alternative for more effective and greener extraction method than conventional organic solvent.

Declaration of Competing Interest

The authors have declared no conflict of interest.

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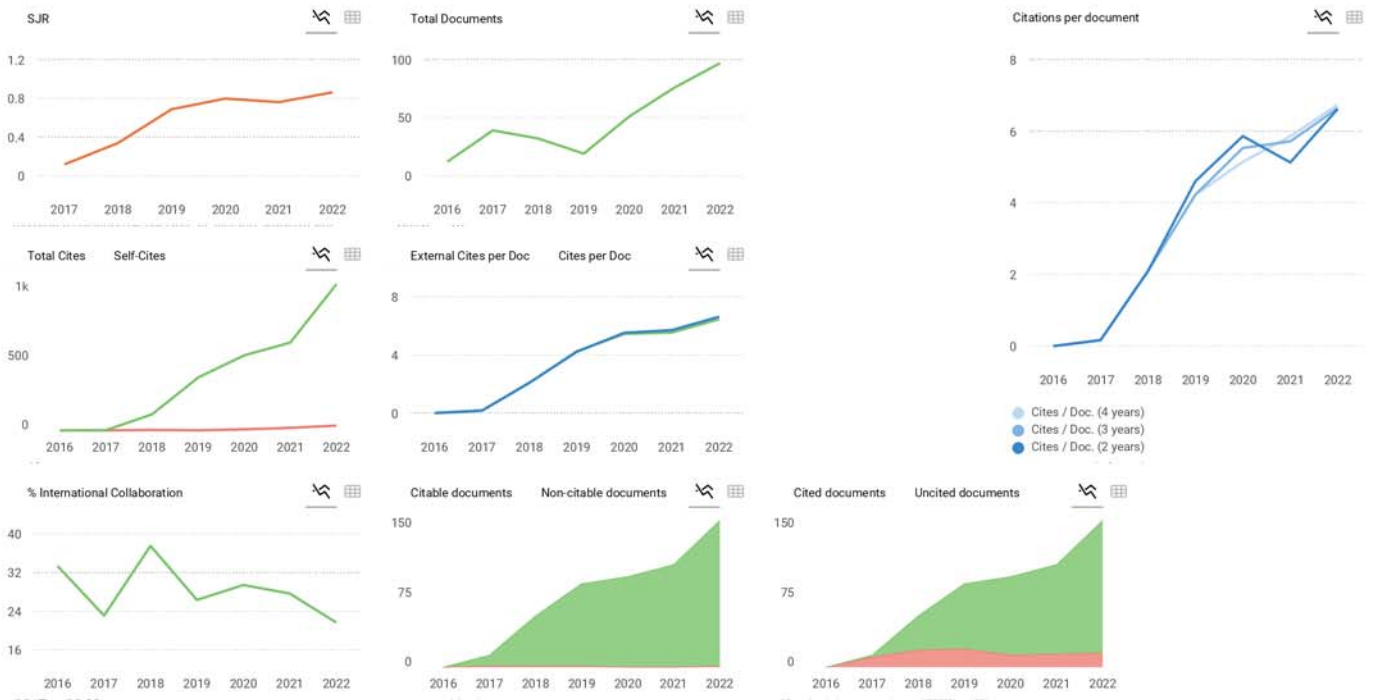
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