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Optimization of ionic liquid-based microwave-assisted extraction of polyphenolic content from *Peperomia pellucida* (L) kunth using response surface methodology

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ABSTRACT

Objective: To optimize the ionic liquid based microwave-assisted extraction (IL-MAE) of polyphenolic content from *Peperomia pellucida* (L) Kunth.

Methods: The IL-MAE factors as experimental design parameters, including microwave power, extraction time, ionic liquid concentration, and liquid–solid ratio had been involved. Response surface methodology and Box–Behnken design were used to obtain predictive model (multivariate quadratic regression equation) and optimization of the extraction process. The response surface was analyzed by using the yields of total polyphenolic content as response value.

Results: Based on the obtained results the optimum extraction condition, including microwave power of 30% Watts, extraction time of 18.5 min, the ionic liquid concentration of 0.79 mol/L, and the liquid–solid ratio of 10.72 mL/g 1-Buthyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) as a solvent was selected. The regression model was obtained to predicts the yields from *Peperomia pellucida*: $Y = 30.250 - 1.356X_1 + 2.655X_2 + 2.252X_3 - 0.565X_4 + 0.990\ X_1X_3 - 8.172\ X_1X_4 - 3.439\ X_3X_4 - 4.178\ X_1^2 - 3.210\ X_3^2 - 6.786\ X_4^2 - 7.290\ X_1^2X_3 + 5.575\ X_1X_3^2 - 4.843\ X_3^2X_4$ with $R^2 = 0.82519$. Scale-up confirmation test was obtained the maximum yields of total polyphenolics content with the amount of 31.172 5 μg GAE/g.

Conclusions: The IL-MAE method produced a higher extraction polyphenolic and performed rapidly, easily and efficiently.

1. Introduction

Bioactive compounds from a natural product (secondary metabolites) produced through the biological pathways in the metabolism of a variety of biosynthetic pathways [1]. It is obtained using the conventional or non-conventional methods [2,3]. A variety of advanced extraction techniques continues to be made to find innovative and efficient extraction methods for the target compound to minimize the extraction time and the solvent usage to provide a higher yield purposes [4,5]. The high-tech extraction methods, such as ultra-high pressure, ultrasound, supercritical fluid, negative-pressure cavitation-assisted, microwave-assisted extraction [4,6–8], and so on are used. Although all of the methods have particular requirements, moreover in some cases, a comparative analysis of these methods has been performed.

Election of the solvent with the approach of green chemistry principles in exploring the content and the active compound potential from natural products continue to rise [8]. The ionic liquids as a solvent have the flexibility of cations and anions combination to adjust the physicochemical properties of the target compound and have the possible substituents to replace

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of the conventional organic solvent that is flammable, volatile, and toxic while the ionic liquids have the different properties [9]. In addition to the physicochemical properties of ionic liquids that affect the extraction, some other considerations about the whole process, the economic, and the environmental impact must also be considered [7]. Some studies have reported the application of ionic liquid for secondary metabolites compound extraction from natural products, such as gallic acid extraction on *Suaeda glauca* Bge. leaves [10], extraction of anthraquinone from *Rheum palmatum* L. [11], extraction of the alkaloid phenolic from *Glaucium flavum* Cr [12,13], and extraction of polyphenolic from *Psidium guajava* [14].

P. pellucida (L) Kunth *(P. Pellucida)* (Piperaceae) is a plant and has a potential activity such as gastroprotective [15], anti-inflammation [16], antimicrobial, antisickling, antioxidant [17–19], and angiotensin converting enzyme (ACE) inhibitor [19]. Several polyphenolic contents have been reported from this herb including, patuloside A [20], dillapiole [21], peperomins [22], pelucidin A [23], chromene [24], and quercetin [19]. Traditionally, this herb is used by the community to treat various diseases such as gout, hypertension, diabetes mellitus, and pain (abdominal pain) [25]. However, to utilize of this plant as a medicinal herb for a production scale purpose has many constraints, especially the yield obtained using conventional extraction methods below one percent. Therefore, the approach of green chemistry principles conducted to develop extraction methods with the aim to increase the yield of active compounds, especially polyphenolic compound. The use of ionic liquid as a solvent combines with microwave technology in the field of extraction and separation secondary metabolites from this plant has been reported in the preliminary study previously [26]. Moreover, based on the best our knowledge, until now, optimization of polyphenolics extraction using ionic liquid based microwave-assisted extraction have not reported.

This study explored the potential of different combinations of ionic liquid based on cations and anions different as a media of microwave absorption. The parameters of extraction include the concentration of ionic liquid (mol/L), the solid–liquid ratio (mL/g), extraction time (minute), and microwave power (%Watt). The IL-MAE method used to the extraction of polyphenolic content from *P. pellucida* and optimized using response surface methodology. The study aims to obtain the optimal of non-conventional extraction method by ionic liquid based microwave-assisted to the extraction of polyphenolic content from this herbs.

2. Materials and methods

2.1. Chemicals and reagents

The chemicals and reagents were used in this study including, Gallic acid standard, Sodium carbonate, and Folin–Ciocalteu which were purchased from Sigma–Aldrich, Germany. [bmim]Cl (1-buthyl-3-methylimidazolium Chloride), [bmim]Br (1-ethyl-3-methylimidazolium bromide), [emim]Br (1-buthyl-3-methylimidazolium bromide), and [bmim]BF_4 (1-buthyl-3-methylimidazolium tetrafluoroborate) were purchased from Chen Jie Chemical Co.Ltd, Shanghai, China. Aqua demineralisation, methanol for analysis, *n*-hexane for analysis, and ethyl acetate (for analysis) were purchased from SmartLab Indonesia.

2.2. Plant materials and sample preparation

P. pellucida (L) Kunth herbs were collected from Nort Mamuju, West Sulawesi Province, Indonesia (from October to December 2016). The voucher specimens were identified at the Herbarium Bogoriense, Botanic Garden, Bogor, West Java, Indonesia. The fresh sample was washed with tap water to remove impurities on the sample surface and was dried using drying ovens (Memmert, Germany) at (50–60) °C temperature. The dried sample was powdered using a grinder (Blender Phillips HR-2874, Phillips Indonesia). The powder obtained was stored at cool temperature until analysis.

2.3. Extraction procedure

2.3.1. Conventional reference extraction methods

The dried powder sample (3 g) was macerated with 50 mL ethyl acetate, allowed to stand for 24 h and extraction performed three times. After that, extractant and residue were separated by filtration and were evaporated to obtain a dry extract.

2.3.2. Ionic liquid based microwave-assisted extraction (IL-MAE)

The IL-MAE method was conducted based on a previous study [26]. Briefly, the dried of powder samples (3 g) was mixed with an ionic liquid solvent then extracted using a microwave-assisted extraction (Modena 900 Watt, with slight modification) which operated under some conditions. The extract solution and residue was separated by filtering using a cotton swab and cooled. The obtained extract solution was left for 10–12 h to precipitate the desired extract.

2.3.3. Determination of total polyphenolic content

The total polyphenol content determination was performed using a microplate reader 96 well method [27–29], with modification. A total of 20 µL of the sample solution or the standard solution were added to 100 µL reagent 25% Folin–Ciocalteu solution, homogenized for 1 min and then allowed to stand for 4 min. Then a 75 µL sodium carbonate solution was added and homogenized for 1 min. Absorbance was measured at a 750 nm wavelength using a microplate reader 96 well (VersaMax™ ELISA Microplate Reader, USA) after incubation for 2 h at room temperature in the dark. Gallic acid solution (200, 100, 50, 25, and 12.5 µg/L, respectively) was used as standards.

The yield of GAE in extracts was determined by comparison of absorbance with standards. The calibration curve of standards (gallic acid) was measured by the absorbance from microplate reader instrument and was calculated using SoftMax 6.5.1 software. The equation formula was $Y = 0.023 + 7.812\ X$ and $R^2 = 0.999$, where Y is the yield of GAE (total polyphenolic content) and X is the absorbance of gallic acid or samples.

2.3.4. Experimental design using response surface methodology (RSM)

Optimization of an IL-MAE method was performed by RSM, which can estimate the interactions between factors and process parameters (independent parameters) on the yield of GAE (dependent parameter). The experiment was applied using a Box–Behnken design (four-factor-three-level), requiring 29 experiments (carried out in triplicate) for the extraction parameters

Table 1
The experimental design of RSM with BBD using [bmim][BF4] as a solvent.

Factors	Unit	Symbol	Range and level (xi)		
			−1	0	1
Extraction time	Min	X_1	10	15	20
Microwave power	%	X_2	10	30	50
Ionic liquid concentration	mol/L	X_3	0.2	0.7	1.2
Liquid–solid ratio	mL/g	X_4	10	12	14

optimization (Table 1). The independent parameters were extraction time (10–20) min, microwave power (P10–50 % Watts), the liquid–solid ratio (10–14) mL/g, and ionic liquid concentration (0.2–1.2) mol/L, and also, the dependent parameter was the yield of GAE. A regression model was calculated based on the actual data from the process parameters and the yield of GAE by the multilinear quadratic model using Design-Expert v10 software licensed (Statease Inc. Minneapolis, MN, USA).

3. Results

3.1. Total polyphenolic content determination

The extraction process was carried out using conventional and nonconventional that aims to obtain the optimal extraction method with secondary metabolite targeted. Based on the results of absorbance measurements from the samples obtained by maceration and IL-MAE methods, differences were found in the yields of total polyphenolic content. The yields of total polyphenolic content from both conventional and non-conventional extraction methods were 16.147 μg GAE/g (ethyl acetate), 33.577 μg GAE/g ([bmim]BF_4), 15.734 μg GAE/g ([bmim]Br), 13.750 μg GAE/g ([Emim]Br), and 15.670 μg GAE/g ([bmim]Cl), respectively.

3.2. Optimization of IL-MAE method

Four factors with three levels, include extraction time (10, 15, and 20 min), microwave power (10, 30, and 50% Watts), ionic liquid concentration (0.2, 0.7, and 1.2 mol/L), and liquid–solid ratio (10, 12 and 14 mL/g) were developed using RSM with Box–Behnken design. Based on the results obtained by Design-Expert v10 software, it shows the three dimensions of response surface for mutual interaction between factor and process parameters. Response surface plot for the yields of total polyphenolic content of the extracts as a function were constructed according to the equation formula in order to determine the optimum conditions including extraction time to microwave power (extraction time = 15 min), [bmim]BF_4 concentration to extraction time ([bmim]BF_4 concentration = 0.7 mol/L), liquid–solid ratio to extraction time and liquid–solid ratio to [bmim]BF_4 concentration (liquid–solid ratio = 12 mL/g), and the microwave irradiation power was set at 30% Watts. The extraction process in different experimental conditions and the yields were shown in Table 2. The obtained data were examined using the

Table 2
Experimental condition by RSM with BBD of the yields.

Run	Extraction time (Min)	Microwave power (%Watts)	Ionic liquid concentration (mol/L)	Liquid–solid ration (mL/g)	Total polyphenol content (μg/g) actual	Total polyphenol content (μg/g) prediction
	X_1	X_2	X_3	X_4	Y_{actual}	$Y_{prediction}$
1	15 (0)	30 (0)	0.7 (0)	12 (0)	33.577 3	30.725 5
2	15 (0)	10 (−1)	0.2 (−1)	12 (0)	17.185 1	22.717 3
3	10 (−1)	30 (0)	0.7 (0)	14 (0)	27.390 2	24.973 7
4	20 (1)	30 (0)	0.7 (0)	14 (0)	11.219 0	9.634 69
5	10 (−1)	30 (0)	0.7 (0)	10 (−1)	11.190 0	12.987 8
6	15 (0)	50 (1)	0.7 (0)	14 (1)	21.800 5	22.642 9
7	15 (0)	30 (0)	0.2 (−1)	10 (−1)	19.375 5	19.369 5
8	10 (−1)	30 (0)	0.2 (−1)	12 (0)	26.366 1	23.725 7
9	15 (0)	50 (1)	0.2 (−1)	12 (0)	30.188 6	31.125 3
10	20 (1)	30 (0)	1.2 (1)	12 (0)	24.726 9	24.374 0
11	15 (0)	30 (0)	1.2 (1)	14 (1)	11.872 8	14.654 6
12	20 (1)	50 (1)	0.7 (0)	12 (0)	23.930 4	27.354 0
13	20 (1)	30 (0)	0.2 (−1)	12 (0)	32.823 4	22.750 2
14	15 (0)	30 (0)	0.7 (0)	12 (0)	32.759 4	30.725 5
15	15 (0)	30 (0)	0.7 (0)	12 (0)	33.047 4	30.725 5
16	15 (0)	50 (1)	0.7 (0)	10 (0)	25.715 4	28.800 4
17	15 (0)	10 (−1)	1.2 (1)	12 (0)	26.177 7	25.458 5
18	15 (0)	50 (1)	1.2 (1)	12 (0)	32.585 2	27.470 5
19	15 (0)	30 (0)	0.2 (−1)	14 (1)	15.439 2	21.890 0
20	15 (0)	30 (0)	0.7 (0)	12 (0)	32.759 4	30.730 0
21	10 (−1)	50 (1)	0.7 (0)	12 (0)	32.478 5	29.305 6
22	10 (−1)	30 (0)	1.2 (1)	12 (0)	14.308 5	21.388 2
23	20 (1)	30 (0)	0.7 (0)	10 (−1)	27.703 1	30.337 1
24	15 (0)	10 (−1)	0.7 (0)	10 (−1)	25.527 0	21.691 2
25	15 (0)	10 (−1)	0.7 (0)	14 (1)	25.210 5	19.132 2
26	10 (−1)	10 (−1)	0.7 (0)	12 (0)	21.686 7	21.039 0
27	20 (1)	10 (−1)	0.7 (0)	12 (0)	19.051 9	25.000 7
28	15 (0)	30 (0)	0.7 (0)	12 (0)	31.824 3	30.725 5
29	15 (0)	30 (0)	1.2 (1)	10 (−1)	29.566 3	25.891 4

Table 3

Analysis of variance (ANOVA) for response surface by quadratic model.

Source	df	Sum of squares	Mean square	F-value	P-value Prob > F
Model	13	1147.027 0	88.233 0	5.455 40	0.001 276
X_1	1	14.702 0	14.702 0	0.909 00	0.355 490
X_2	1	84.587 0	84.587 0	5.230 00	0.037 150
X_3	1	40.561 0	40.561 0	2.507 90	0.134 130
X_4	1	2.553 0	2.553 0	0.157 90	0.696 730
X_1X_3	1	3.923 0	3.923 0	0.242 50	0.629 510
X_1X_4	1	267.131 0	267.131 0	16.516 6	0.001 020
X_3X_4	1	47.316 0	47.315 0	2.925 60	0.107 790
X_1^2	1	117.441 0	117.441 0	7.261 33	0.016 630
X_3^2	1	69.325 0	69.325 0	4.286 30	0.056 090
X_4^2	1	309.824 0	309.824 0	19.156 00	0.000 540
$X_1^2X_3$	1	141.727 0	141.727 0	8.762 90	0.009 730
$X_1X_3^2$	1	82.869 0	82.869 0	5.123 76	0.038 860
$X_3^2X_4$	1	62.534 0	62.534 0	3.866 42	0.068 050
Residual	15	242.602 5	16.173 5	–	–
Lack of Fit	11	154.740 0	14.067 3	0.640 42	0.747 700
Pure error	4	87.862 5	21.965 6	–	–
Cor total	28	1389.629 2	–	–	–

multivariate regression analysis. The regression model was obtained that predicts the yields from *P. pellucida* with the equation formula as follows:

$$Y = 30.250 - 1.356X_1 + 2.655X_2 + 2.252X_3 - 0.565X_4 + 0.990X_1X_3 - 8.172X_1X_4 - 3.439X_3X_4 - 4.178X_1^2 - 3.210X_3^2 - 6.786X_4^2 - 7.290X_1^2X_3 + 5.575X_1X_3^2 - 4.843X_3^2X_4$$ with $R^2 = 0.82519$

Where Y is yields of total polyphenolic content, X_1 is factor A (extraction time), X_2 is factor B (microwave power), X_3 is factor C (ionic liquid concentration), and X_4 is factor D (liquid–solid ratio).

In Table 3, the correlation coefficient (R^2 = 0.825 19) obtained from the calculation model which implies more than 82.518% of the variation can be expressed using this model, and *F*-value for lack of fit ($P > 0.05$) was 0.64 which shows no significance of the real error. The significance of the *F* value of 0.747 7 lack of fit with $P > 0.05$ was not significant, or over 74.77% occurs because the response surface factor used. *F* value of model was 5.45 which indicates the model was significant, and 0.13% probability *F* value of model occur as disorders. All the above analysis results explain the acceptableness of the model. Prob > *F* value smaller than 0.05 also implies this model was significant.

4. Discussion

This study was demonstrated that [bmim]BF_4 solvent can extract the secondary metabolites with highest total polyphenolic content than the other ionic liquid solvent. From the above results, we saw that [bmim]BF_4 was more effective as a solvent compared to other. The solvent of [bmim]BF_4 was twice higher than ethyl acetate solvent (a solvent widely used in the previous researches with this plant). The ionic liquid solvent of [bmim]BF_4 could produce satisfactory secondary metabolites with the highest total polyphenolic content than the other ionic liquid solvent. It might be caused to extraction capability that strongly related to the hydrophobicity of ionic liquids [15,30]. Improved ability to attract certain chemical components can increase with an increase in the hydrophobicity of the solvent [32]. In our work, the four of ionic liquids were used have different the hydrophobicity properties namely [emim]Br < [bmim]Br < [bmim]Cl < [bmim]BF_4 [30], respectively. Moreover, the hydrogen bonding capabilities of ionic liquids are factors affecting the extraction by considering the anion [31,34]. According to the literature, [bmim]BF4 has been reported that it is effective as a solvent for extracting polyphenolic compounds from plants [32,33].

Some parameter of extraction condition as an independent variable was used to optimize the IL-MAE method (*i.e.*, the concentration of [bmim]BF4, liquid–solid ratio, extraction time, and microwave power), which might extensively affect the efficiency of extraction. In this work, the parameters of extraction condition were optimized based on the extraction efficiency of the yields of total polyphenolic content as a dependent variable in this herbs, as some studies had reported that the compounds were responsible for the pharmacological properties of this herb [16–21]. In addition, to compare with standard compounds is difficult because it is not commercially available except obtained by isolating it.

Effect of extraction time on the range from 10 to 20 min examined to find the optimal of extraction. In this study, the optimum times obtained in extraction for 15 min adequate to extracting secondary metabolites with the highest polyphenol content while decreasing the total phenol content occurred after 15 min. This condition means that the dissolution of solutes from the plant matrix occurs equilibrium concentration of secondary metabolites in 15 min [35].

Effect of Microwave power was on the range from 10% to 50% Watts. The higher of microwave power gave the higher of the yields produced. The increase in temperatures that are too high can cause damage to the sample matrix and can also cause changes in the structure of the targeted compound. By considering the temperature and stability of the ionic liquid and content of secondary metabolites, the microwave power of 30 %Watts was seen as sufficient capable to extracting the secondary metabolites maximally.

Effect of ionic liquid concentration was on the range from 0.2 to 1.2 mol/L. The optimum yield was obtained at a concentration of 0.7 mol/L. The concentration effect was associated with the viscosity levels making it difficult to penetrate the cell wall damage. Also, it has a significant role in reducing operational costs.

The liquid–solid ratio is other factors influencing the process of extraction. A large ionic liquid ratio could lead the ineffective extraction process, and a little ionic liquid could lead the imperfective extraction process. A variety of the ratio of liquid–solid was performed in the range of (10–14) mL/g on the extract yield. The maximum extraction to the yields obtained at 12 mL/g.

The optimum condition was suggested based on the results of RSM analysis using Design-Expert v10 software as follows; extraction time of 18.5 min, microwave power of 26.47% Watts (or ~30% Watts), 0.79 mol/L [bmim]BF_4, and the liquid–solid ratio of 10.72 mL/g. For scale-up confirmation test, a 30 g sample was extracted using the optimum condition and was obtained the maximum yield of total polyphenolic content with the amount of 31.172 5 μg GAE/g.

This study is an early stage in the development of extraction methods to obtain biomarker from medicinal plants rapidly, easily, and efficiently. Furthermore, the further study is in progress including the optimization of extraction procedure in pilot scale, isolation of biomarker or active compound, and

screening of angiotensin converting enzyme (ACE) inhibitory activity.

P. pellucida is one of the plants which has many benefits and is rich in polyphenols. However, until now this plant is not fully utilized. Therefore, the application of IL-MAE method has been carried out for extracting polyphenols from this plant. In this study, the optimum condition was developed for extraction the maximum polyphenolic content using RSM analysis. This method produced a higher extraction polyphenolic and performed rapidly, easily and efficiently. These results expected to contribute to the development and utilization of the plant as a raw material of herbal medicines.

Conflict of interest statement

We declare that we have no conflict of interest.

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