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Ionic liquid-based ultrasonic-assistedextraction model for solvent design

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Abstract. Ionic liquid is a favourable solvent in separation process due to the vast possibilities of ionic liquid structures. Many researches showed that ionic liquid extract higheramount of phytochemicals compared to conventional solvents. Even better, ionic liquid extraction coupled with ultrasonic-assisted extraction produced higher yield and less hassle. Therefore, ionic liquid can be considered as a suitable solvent for herbal extraction. This study is a part of a solvent design framework to obtain an extraction process model. It focuses on the process of ionic liquid-based ultrasonic-assisted extraction of flavonoid and phenolic acid from *Labisiapumila*. A two level, four factor of central composite design (CCD) was employed to determine the effect of the process factors towards yield of flavonoid and phenolic acid extracted from the herb. The process factors are the temperature (Celsius), extraction time (min), power (W) and type of ionic liquid (based on their dielectric point). The extracted samples were analysed to determine the yield of flavonoid and phenolic acid. Two models were developed for flavonoid and phenolic acid extraction based on the optimization results. The models are important as yield prediction in solvent process performance stage of the development of ionic liquid design framework.

1. Introduction

Phytochemicals are bioactive compounds that are responsible for medical properties of plants [1]. These wide rangesof bioactive compounds mainly act as natural antioxidants and categorized into different types of terpenoids, alkaloids, flavonoid and phenolic acid [2]. Medical or herbal plants have been used traditionally all over the world to treat ailments and as a healthy choices of food sources [3]. Extraction methods are important in determining the amount and quality of end products from this herb [4]. Many factors can influence herbal extraction process especially the type of solvents used in the process [5]. Herbal extraction process mainly used conventional organic solvents in the market. However, these solvents can be harmful to humans, easily volatile and have lower selectivity. Therefore, it is important to find an alternative solvent replacing organic solvent in the process.

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Ionic liquid is one of the suitable alternative solvents in the market nowadays. It has been recognized as an efficient solvent in separation processes [6] and has opposite properties from conventional solvents [7]. Ionic liquid also able to be recycled without affecting its unique quality thus reduce solvent loss during the extraction process. Nowadays, ionic liquid has been widely used in azeotropic separation [8] and carbon capture [9]. Ionic liquid is favourable as their molecules (anion, cation, alkyl chain and other substituents) can be tailored according to a specific application [10]. However, this can be a huge challenge in selecting ionic liquid for certain applications due to huge possibilities of different ionic liquid molecules interactions.

Therefore, systematic approach and predictive thermodynamic models can be used to reduce the challenge in selecting optimal ionic liquid. This method also simplifies and reduce experimental cost in any process. This approach usually considers the molecular structure and their interaction with the target molecules as well as thermo-physicochemical properties of ionic liquid.

This study is a part of a framework ionic liquid solvent design. It focuson optimizing the extraction parameters of ionic liquid-phytochemical extraction using an ultrasonic-assisted method and finally develop a model of herbal phytochemical extraction process. The ionic liquid used in this research were selected from previous research [11] using solvent design framework. Phytochemicals selected for this study are flavonoid and phenolic as these are the main antioxidant compounds found in many plants.

2. Methodology

2.1.Solvent design

This study is part of an ionic liquid design using computer-aided molecular design (CAMD) approach. A framework of ionic liquid selection was developed based on target properties and constraints. In this framework, ionic liquid and phytochemical properties databases, as well as property models' library were developed for screening purposes. Unknown property value or data due to unlimited possibilities of ionic liquid structures were solved by applying property prediction.The extraction process model developed in this study are to be used in this solvent design. It is to predict the yield/solubility of phytochemicals when using ultrasonic-assisted method, therefore reduce the possible candidates in the design.Finally, three ionic liquid candidates were selected based on the target and cost values.

2.2.Reagents and equipment

The standard chemicals of quercetin and gallic acid were purchased from Merck (Germany). Ethyl acetate and methanol purchased from HmbG GmbH; ionic liquid (1-butyl-3-methylimidazolium bromide, 1-butyl-3-methylimidazolium chloride and 1-ethyl-3-methylimidazolium tetrafluoroborate) obtained from Sigma Chemical.

Table 1. Optimized parameters for ionic liquid ultrasonic-assisted extraction

Factors		Unit	Value range
A	Ionic liquid	Farad per meter (Σ)	3.59 - 13.6
B	Temperature	Celsius (^{o}C)	35 - 45
C	Irradiation time	Minutes (min)	1 - 10
D	Irradiation power	Watt (W)	250 – 450

2.3. Plant materials and extractions

*Labisiapumila*or Kacip Fatimah were purchased from EthnoHerbs Sdn. Bhd. The leaves and branches were oven dried and made into coarse powder. In this study, 0.3 g of dried powder were mixed with 3 ml of ionic liquid in a test tube for 10 min and inserted into an ultrasonic bath for extraction. To improve the yield of end-product, different parameters (Table 1) were optimized using Response Surface Method (RSM) with two level, four factor of central composite design (CCD). Factor A is based on the dielectric value of ionic liquid 1-butyl-3-methylimidazolium bromide, 1-butyl-3-methylimidazolium chloride and 1-ethyl-3-methylimidazolium tetrafluoroborate where the values are 3.59, 3.85 and 13.6 respectively. After each extraction, the extracts were separated from the herbs. The extraction yield conveyed as mg of target ingredient extracted per g of sample.

2.4. Determination of total flavonoid content

The aluminium chloride colorimetric method to determine total flavonoid content is based on [12]. Quercetin was used to make the calibration curve. 10 mg of quercetin was dissolved in 10 ml of methanol and diluted to six different concentrations. 0.5 ml of diluted solution were separately mixed with 1.5 ml of 95 % ethanol, 0.1 ml of 10 % aluminium chloride, 0.1 ml of 1M potassium acetate and 2.8 ml of distilled water. The mixture was incubated in about 30 min and the absorbance was measured at 415 nm with a Shimadzu UV-160A spectrophotometer. The amount of 10 % aluminium chloride was substituted by the same amount of distilled water in blank. The amount of total flavonoid compounds was expressed as mg quercetin/g dry weight of the plant material. The data were presented as the average of triplicate analyses.

2.5. Determination of total phenolic acid content

Total phenolic content measured based on the standard procedure of Folin-Ciocalteau method [13]. Gallic acid used as standard reference for total phenolic content. 1 mg of gallic acid were dissolved in 1 ml of methanol and diluted to different concentrations. 0.1 ml of the diluted solution were transferred and made up to 4.6 ml with distilled water. After addition of 0.1 ml Folin–Ciocalteu reagent and 0.3 ml of 2 % Sodium Carbonate (Na_2CO_3). The mixture was incubated for 45 min in a dark room and vortexed before measurement of absorbance at 760 nm. The amount of total phenolic content was expressed as mg gallic acid (GAE)/g dry weight of the plant material. The data were presented as the average of triplicate analyses.

3. Results and discussions

3.1. Effect of different extraction solvents

This study used three different types of ionic liquids and ethyl acetate as a control solvent for flavonoid and phenolic acid extraction from *L. pumila.* During constant condition of extraction process (temperature 35 ^{o}C, 250 W of ultrasonic power in 10 min), it can be observed that ionic liquid produces higher yield compared to ethyl acetate. Figure 1 showed that 1-butyl-3-methylimidazolium chloride ([BMIM][Cl]) was the best extraction solvent for both compounds compared to other ionic liquids. Ionic liquid makes a better extraction solvent due to the molecular structure of their anion and cation.

The length of alkyl chain of ionic liquid cation positively influences the extraction yield but simultaneously increases the hydrophobicity of the ionic liquid with the increase of alkyl length. Both the proper hydrogen bonding and hydrophobic interactions resulted in stronger solvation interactions with flavonoids and phenolic acids. The best solvents have good selectivity and capacity, high thermal stability, good availability, low cost, high surface tension and low to moderate viscosity [14]. Selectivity and solubility are highly dependent on composition thus it depends on the extraction temperature and irradiation power [15].

3.2. Development of yield prediction model

The objective of the study is to optimize the ionic liquid ultrasonic-assisted extraction conditions and to find the relations between the factors involved. Parameters involved were analyzed statistically using Design Expert 7.0 software by two-level, four-factor of central composite design (CCD). The analysis resulted in two different process models for the extraction of flavonoid and phenolic acid using ionic liquid-based ultrasonic-assisted extraction. In this analysis, quadratic model was used as a base to analyse parameter interactions and developed a process model.

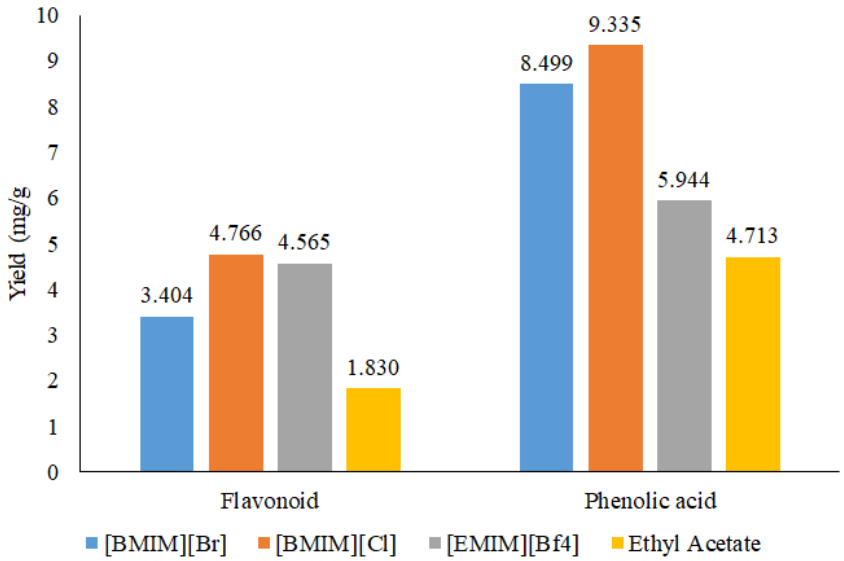

Figure 1. Effect of four different solvents on the extraction of quercetin and gallic acid.

Table 2 explained the ANOVA analysis for each of the factors of flavonoid extraction from *L. pumila*. In terms of the model's F-value of 26.08, it implies that the model is significant. There is only a 0.01 % chance that a model this large could occur due to noise. Based on the statistical value, P-value less than 0.05 indicates that the parameters are significant. In this case, the extraction parameters of A, B, C, D and interaction parameters of AC, A^2 and B^2 are significant model terms. The F-value for Lack of Fit was 4.33 implies there is a 5.96 % chance that a "Lack of Fit F-value" this large could occur due to noise. The lack of fit value is not significant indicates that the model can be fitted.

Table 2. ANOVA analysis for Response Surface Reduced Quadratic Model for Flavonoid Extraction

	Mean Square	F Value	Prob.> F
Model	0.18	26.08	< 0.0001
A-dielectric value	1.3	184.23	< 0.0001
B-Temperature	0.045	6.38	0.0233
C-Time	0.12	17.3	0.0008
D-Power	0.05	7.04	0.0181
AB	1.49×10^{-3}	0.21	0.003
AC	0.096	13.51	0.0022
A^2	0.67	94.38	< 0.0001
B^2	0.094	13.27	0.0024
Lack of Fit	9.52×10^{-3}	4.33	0.0596

ANOVA analysis for phenolic acid extraction factors of *L. pumila* is shown in Table 3. In terms of the model's F-value of 44.84, it implies that the model is significant. There is only a 0.01 % chance that a model this large could occur due to noise. In this case, parameters A, B, C and D as well as parameter interactions of AB, AD, BD and A^2 are significant model terms. The F-value for Lack of Fit was 5.94 implies there is a 94 % chance that a "Lack of Fit F-value" this large could occur due to noise. Therefore, it can be concluded both models constructed is suitable.

Table 3. ANOVA analysis for Response Surface Reduced Quadratic Model for Phenolic Acid Extraction

	Mean Square	F Value	Prob.> F
Model	0.1	44.84	< 0.0001
A-dielectric value	0.031	13.37	0.0015
B-Temperature	0.21	92.6	< 0.0001
C-Time	0.011	4.94	0.0374
D-Power	0.32	138.08	< 0.0001
AB	0.042	17.97	0.0004
AD	0.06	26.13	< 0.0001
BD	0.082	35.34	< 0.0001
A^2	0.041	17.67	0.0004
Lack of Fit	2.88×10^{-3}	5.94	0.94

Table 4. Statistical value for quadratic model equation of ionic liquid ultrasonic-assisted extraction process

Flavonoid		Phenolic Acid	
Std. Dev.	0.084	Std. Dev.	0.048
R-Squared	0.96	R-Squared	0.94

Based on the R-squared predicted by the software, thefit model ofquercetin and gallic acid extraction have high value reaching to value of 1. R-squared illustrate how good your model is, when compared to the baseline model. Based on the value, model for flavonoid extraction have R-squared valued of 0.96 and phenolic acid extraction achieved R-Squared 0.94. Thus, it can be assessed that both modelsare a good fit. Since the value of lack of fit and the R-squared value are in a suitable range, thus it can be said that the quadratic models for gallic acid and quercetin extraction that were developed are suitable for the use of phytochemicals extraction prediction. The Equations (1) and (2) will be used as process model to improve the ionic liquid design framework in process performance stage.

Yield of flavonoid

$$[7.38 + 0.27\,(\mathrm{A}) + 0.05\,(\mathrm{B}) + 0.083\,(\mathrm{C}) + 0.053\,(\mathrm{D}) + 9.20\,\mathrm{x10} - 3\,(\mathrm{AB}) - 0.074\,(\mathrm{AC}) + 3.14\,\mathrm{x10} - 4\,(\mathrm{AD}) + 4.94\,\mathrm{x10} - 3\,(\mathrm{BC}) + 1.12\,\mathrm{x10} - 3\,(\mathrm{BD}) - 2.02\,\mathrm{x10} - 3\,(\mathrm{CD}) - 5.33\,(A^2) - 0.19\,(B^2) + 2.23\,\mathrm{x10} - 3\,(C^2) + 0.094\,(D^2)]^2 \quad (1)$$

Yield of phenolic acid

$$[3.78 - 0.041\,\mathrm{A} + 0.11\,\mathrm{B} + 0.025\,\mathrm{C} + 0.13\,\mathrm{D} + 0.049\,\mathrm{AB} + 0.059\,\mathrm{AD} - 0.071\,\mathrm{BD} - 0.87\mathrm{A2}]^2 \quad (2)$$

4. Conclusion

Ionic liquid solvents coupled with ultrasonic-assisted extraction is efficient to produce higher yield of end-product. Aside from product quantity and quality, ionic liquid can be recycled and reused for the process thus more sustainable. In this study, two significant extraction process models have been developed for herbal extraction using ionic liquid and ultrasonic extraction. The models developed can be the baseline for herbal extraction process using ionic liquid and ultrasonic-assisted method in predicting the yield of end-product. These models will be used to improve the development of ionic liquid design framework by assisting in ionic liquid selection in process performance stage.

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