Journal of Applied Pharmaceutical Science Vol. 7 (10), pp. 023-029, October, 2017
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2017.71004
ISSN 2231-3354

Comparison of Ionic Liquid-Microwave-Assisted Extraction and MAE of Resveratrol from Melinjo (*Gnetum gnemon* L.) Seeds

Maesya Rachmawati[1], Imalia Nurrachma Ayuningtyas[1], S. Sutriyo[2], Abdul Mun'im[3*]

[1]Graduate Program of Herbal Medicine, Faculty of Pharmacy, Universitas Indonesia, Depok 16424 West Java, Indonesia.
[2]Department of Pharmaceutical Technology, Faculty of Pharmacy, Universitas Indonesia, Depok 16424 West Java, Indonesia.
[3]Department of Pharmacognosy-Phytochemistry, Faculty of Pharmacy, Universitas Indonesia, Depok 16424 West Java, Indonesia.

ARTICLE INFO

Article history:
Received on: 10/07/2017
Accepted on: 16/09/2017
Available online: 30/10/2017

Key words*:* Microwave assisted extraction; melinjo; *trans*-resveratrol; *Gnetum gnemon*; ionic liquid.

ABSTRACT

Purpose**:** This study investigated the effect of [Bmim]Br microwave assisted extraction (MAE), and MAE methods using ethanol on *trans*-resveratrol extraction from Melinjo (*Gnetum gnemon*) seeds.
Methods**:** The three-level response surface methodology was used to optimize extraction conditions for *trans*-resveratrol content from Melinjo seeds using MAE method and IL-MAE. Resveratrol content was determined using HPLC, and antioxidant activity was examined by DPPH assay.
Results**:** Compared to the MAE-ethanol method, then the optimum result of IL-MAE was reached with [Bmim] Br concentration 2.5 mol/L; microwave power 10%; and extraction time 10 min with the *trans*-resveratrol value 0.52 mg/g. The antioxidant activity value of IL-MAE melinjo seed extract was in 82.82% of DPPH inhibition.
Conclusion**:** This IL-MAE method was suitable to apply as an alternative technique to extract the active compound from the plant.

INTRODUCTION

Melinjo (*Gnetum gnemon* L) is a plant that grows in many areas of Indonesia, especially Java Island. People in Indonesia is commonly use almost all parts of plant melinjo such as leaves, flowers, and fruits. Melinjo seed was usually used as a raw material to make a foodstuff called "emping cracker" while melinjo peel usually only processed into the vegetable but mostly as a waste (Barua *et al*., 2015) Several researchers reported that resveratrol as an active compound contain in the melinjo seeds were also naturally occurred in 72 plant species such as grapes, it also contained in peanuts (Limmongkon *et al*., 2017), fruits like blackberries or raspberries (Vinas *et al*., 2008), rhizome of *Rheum undulatum* (Matsuda *et al*., 2000) and more recently in chocolate (Counet *et al*., 2006). *Trans*-resveratrol is a natural polyphenolic compound with stilbene structure. *Trans*-resveratrol could be accumulated in a plant as an effect of plant resistance mechanism to parasites and other inconvenient effect such as UV radiation, chemical substances, fungi or bacteria (Jeandet *et al*., 2017). There is two geometric structure of resveratrol, the *trans*- and *cis*-configured isomers. *Trans*-resveratrol (3,5,4'-trihydroxystilbene) has been proved to have some therapeutic effects, especially for its antioxidant activities (Gulcin, 2010). Conventional method requires a lot of solvents, the resulting low extraction efficiency, and a long time of extraction process. Therefore it is necessary to find more effective and efficient as an alternative method for extraction of a biological compound (Mandal *et al*., 2007). Microwave-Assisted Extraction (MAE) is one of alternative extraction technique which is fast and efficient, easy to use, has a good selectivity, it also has a low instrument set up a cost for laboratory scale. MAE could be categorized as a green technique because of its advantages of decreasing solvent waste and solvent release into the environment (Wang and Weller, 2006; Kaur *et al*., 2016; Destandau *et al*., 2016).

* *Corresponding Author*
Abdul Mun'im, Department of Pharmacognosy-Phytochemistry, Faculty of Pharmacy, Universitas Indonesia, Depok 16424 West Java, Indonesia. Tel: + 62 8111184550. E-mail: abdul.munim61@ ui.ac.id

MAE has been successfully used to extract bioactive compound with both organic solvent and also ionic liquid. Selection of solvent is one of a factor that influences the MAE process. Successful MAE process with an organic solvent should consider the polarity of the solvent. Polar solvent, such as water, methanol or ethanol are usually more extractable than nonpolar (Wang and Weller, 2006).

But in recent years, the unique physical and chemical properties of ILs have attracted considerable attention in analytical chemistry especially in MAE process because of its excellent properties, such as poor conductors of electricity, non-ionizing, highly viscous, low vapor pressure, low combustibility, excellent thermal stability, wide liquid regions and favorable solvating properties for a range of polar and non-polar compounds (Tang *et al*., 2012). It makes IL could be an alternative solvent for extracting the biological compound from the plant.

Some articles showed that IL-assisted MAE has been applied to extract variety classes of compound with an optimum yield such as from *Psidium guajava*, *Smilax china* (Du *et al*., 2009), *Nelumbo nucifera* (Ma *et al*., 2010), *Apocynum venetum* (Tan *et al*., 2016) and *Peperomia pellucida* (Ahmad *et al*., 2017). Besides that, the IL 1-n-butyl-3-methylimidazolium ([Bmim]Br) solution has been published that it successfully extracted *trans*-resveratrol from *Polygoni cuspidatum* (Du *et al*., 2007). There has not been found studies that reporting on optimization of resveratrol extraction methods from *Gnetum gnemon* L. (Melinjo) using MAE method and comparison the extraction efficacy of both organic solvent and [Bmim] Br. So the aim of this study is to determine the optimal conditions of the two solvents to extract *trans*-resveratrol from melinjo seed and how effective the antioxidant activity of melinjo seed extract produced.

The seed part of the plant contains a relatively high lipid. Likewise with melinjo seeds that contain high enough lipid is 16.4% which can interfere with the extraction process. Defatisation is a method that can be used to reduce lipid content so as increasing the extraction results. Defatted kenaf seed meals contain high phenolic-saponin compounds (Chan *et al*., 2014). Defatted annato seeds increase bixin content in annato seed extract (Rodrigues *et al*., 2014). Defatted grape seeds also show a high total phenolic value (Duba *et al*., 2015).

MATERIALS AND METHOD

Plant materials and reagents

Fresh seeds which were used in this study was melinjo seed which was characterized by a red color and yellow seed color. The seed of Melinjo was collected and obtained through drying and shelling. It was purchased in Bogor, West Java. All chemicals reagents used were classified as HPLC grade or higher and sourced from commercial suppliers such as standard *trans*-resveratrol was bought from Sigma-Aldrich Pte. Ltd., (Singapore). Ionic liquid 1-butyl-3-methylimidazolium bromide ([Bmim]Br) (>99%) was obtained from Chengjie Chemical Co., Ltd., (Shanghai, China). The organic solvent such as ethanol, ethyl acetate, methanol, acetonitrile, acetic acid were purchased from Merck, German; n-hexane and demineralized water (Bratachem, Indonesia). DPPH (1,1-diphenyl-2-picrylhydrazyl) from Sigma-Aldrich Pte. Ltd., (Singapore).

Instrumentation

Microwave instrument (Modified Modena MV-3002) with a microwave power of 900 W; refrigerator (Sharp, Japan); vacuum evaporator (Buchi, German); water bath (Imperial®, Australia), Sonicator (Ultrasonic LC 20H), centrifuge (Heraeus-Christ GmbH, Osterode, Germany), vortex (WiseMix VM-10, Daihan Scientific Co., Ltd., Korea), volume pipette (Pyrex), micropipette 100-1000 μl (Thermo Scientific), and 10-100 μl (Thermo Scientific), pH meter (Eutech Instruments, France), HPLC Instrument (Shimadzu, Japan)-UV Detector SPD 20A; and pump LC-20AT, and microplate reader (Versa Max, China).

Sample Preparation

The outer melinjo seed was peeled, washed and dried in the sun for six days. The dried melinjo seeds then crushed using a blender. The powder was first defatted using n-hexane for 24 h, then aerated to remove the n-hexane residue.

Optimization IL-MAE by response surface methodology (RSM)

The response surface methodology with Design-Expert version 10.0 software (Stat Ease Inc., Minneapolis, USA) was used to analyze the interaction between some factors and optimize experimental conditions to get 13 sample of treatment for both solvents.

The independent variables for microwave-assisted extraction of resveratrol included concentration of ethanol (50–90%), IL concentration (0.5–2.5 mol/L), extraction time was varied on several conditions (5 – 15 minute), microwave power of 10, 30 and 50% of 900 W for 100% microwave power supply. The response value of this study was resveratrol yield (mg/g) with ANOVA analysis for the significance of the model.

Extraction Procedure

Melinjo seed was extracted using MAE method with the following condition

MAE with ethanol

The defatted melinjo seeds powders (10g) were extracted using ethanol (1:10 g/mL) with a variety of different extraction conditions such as microwave power (10-50%), irradiation time (5-15 min) and different solvent concentration of ethanol (50-90% v/v).

The boiling flask contains sample with different concentration was placed in a microwave. The obtained ethanol extract solution then filtered and the filtrate was evaporated using rotary vacuum evaporator and then dried in vacuum oven at 40 ^{o}C. Extracts were stored in brown bottles at 4 °C. Optimization condition on extraction was employed by response surface methodology

(RSM), so the extraction conditions were varied to some factors as described in Table 1.

Table 1: Experimental parameters of response surface methodology of MAE with ethanol and resveratrol content.

Run	Ethanol Concentration (%)	Time (min)	Power (%)	Resveratrol yield (mg/g)	
				Predicted	Experimental
1	50.00	5.00	30.00	0.063	**0.048**
2	50.00	10.00	10.00	0.064	**0.039**
3	90.00	15.00	30.00	0.22	**0.235**
4	70.00	5.00	50.00	0.12	**0.086**
5	70.00	5.00	10.00	0.086	**0.126**
6	90.00	10.00	50.00	0.28	**0.31**
7	70.00	15.00	10.00	0.06	**0.098**
8	50.00	15.00	30.00	0.032	**0.019**
9	90.00	10.00	10.00	0.3	**0.25**
10	70.00	15.00	50.00	0.12	**0.081**
11	90.00	5.00	30.00	0.22	**0.23**
12	50.00	10.00	50.00	0.18	**0.235**
13	70.00	10.00	30.00	0.069	**0.069**

[Bmim]Br-MAE

The defatted melinjo seeds powders (1g) were put in a boiling flask and extracted using IL-MAE method. [Bmim]Br solution (1:15 g/mL) with some particular concentration (0.5-2.5 mol/L) was added into the flask, and the extraction process was performed under different power level in a range 10-50% and time of irradiation in 5-15 min. The extracts were centrifuged at 3000r/min for 15 minutes, and then the supernatant was diluted to 10 mL with double distilled water for analysis. Optimization condition on extraction was employed by response surface methodology (RSM) which were varied to some factors as described in Table 2.

Table 2: Experimental parameters of response surface methodology of IL-MAE and resveratrol content.

Run	IL Concentration (M)	Time (min)	Power (%)	Resveratrol yield (mg/g)	
				Predicted	Experimental
1	0.50	10.00	10.00	-0.015	**0.0013**
2	0.50	5.00	30.00	0.031	**0**
3	2.50	5.00	30.00	0.27	**0.152**
4	2.50	10.00	50.00	-0.080	**0.000022**
5	1.50	5.00	10.00	0.37	**0.4045**
6	2.50	10.00	10.00	0.42	**0.5243**
7	2.50	15.00	30.00	0.062	**0.0011**
8	1.50	15.00	10.00	0.032	**0.005**
9	0.50	10.00	50.00	0.014	**0.0016**
10	1.50	10.00	30.00	0.084	**0.0016**
11	1.50	5.00	50.00	-0.064	**0**
12	1.50	15.00	50.00	-1.634E-003	**0**
13	0.50	15.00	30.00	-0.031	**0.0001**

Determination of *trans*-resveratrol

The samples were analyzed for resveratrol content using High Performance Liquid Chromatography (HPLC) method. Each standard and the sample were injected in triplicate into YMC HPLC column (150 mm x 4.6 mm, 5µm). Mobile phase consists of a mixture of water/acetonitrile with volume ratio 75/25 and adjusts to pH 3 by acetic acid, and the elution system was isocratic type at 1.0 mL/min flow rate. The sample was injected in 20 µl, and wavelength was detected at 306 nm through a UV detector LC-20AT (Shimadzu). SPD-20A integrator (Shimadzu) was used to collect chromatogram data.

Preparation of *trans*-resveratrol standard solution

Standard solutions were prepared by diluting the stock solution of *trans*-resveratrol (100 mg/L) with ethanol HPLC grade and double distilled water in the concentration range 2-10 µg/mL.

$$\text{Total } trans\text{-resveratrol content (mg/g)} = \frac{trans\text{-resveratrol amount in extract (mg)}}{\text{melinjo seeds sample amount (g)}}$$

DPPH free radical scavenging activity

DPPH• solution was freshly prepared before the evaluation proceed, stored in a flask covered with aluminum foil, and kept in the dark at 4°C between the measurements. 200 µg/mL solution of DPPH• was prepared in methanol, and 100 µL of this solution was added to 50 µL of the sample solution in methanol. These solutions were shaken thoroughly and incubated in the dark at room temperature for 30 minutes. The optical density of each sample was measured at 517 nm to find out the absorbance of DPPH from the various extract. Radical scavenging activity (RSA) was calculated as below:

RSA (%) = $[(A_0 - A_1)/A_0]$ X 100, where A_0 was the absorbance of pure DPPH and A_1 was the absorbance of DPPH in the presence of various extracts.

RESULTS AND DISCUSSION

The ANOVA statistical analysis

The analysis of variance (ANOVA) carried out to determine the significance of the independent parameters and their interactions, the adequacy of the developed model and statistical significance of the regression coefficients. The ANOVA for optimization of MAE-ethanol calculated that F value is 2.41 and the P-value was 0.25, which means that the model did not significantly affect the response or not significantly affect the resveratrol yield. Some values with a p-value less than 0.05 indicate that model terms are significant. In this case, only solvent concentration with p-value 0.04, that was significantly affected the resveratrol yield ($p>0.05$). That was a different way to the IL-MAE method; the ANOVA calculated that the model F-value 6.12 and the p-value was 0.022 which indicate that the model was significant and acceptable. Furthermore, ANOVA also showed that each independent variables were significantly influenced the resveratrol yield.

The 3D response surfaces for the interaction between two independent variables and response showed in Figure 1. Figure 2a, c, and e showed a relationship between ethanol concentration and power, and time, respectively. Figure 2b, d, and f demonstrated the interaction between variables in the IL-MAE method which is significantly affected to *trans*-resveratrol yield, but the response was not strong enough.

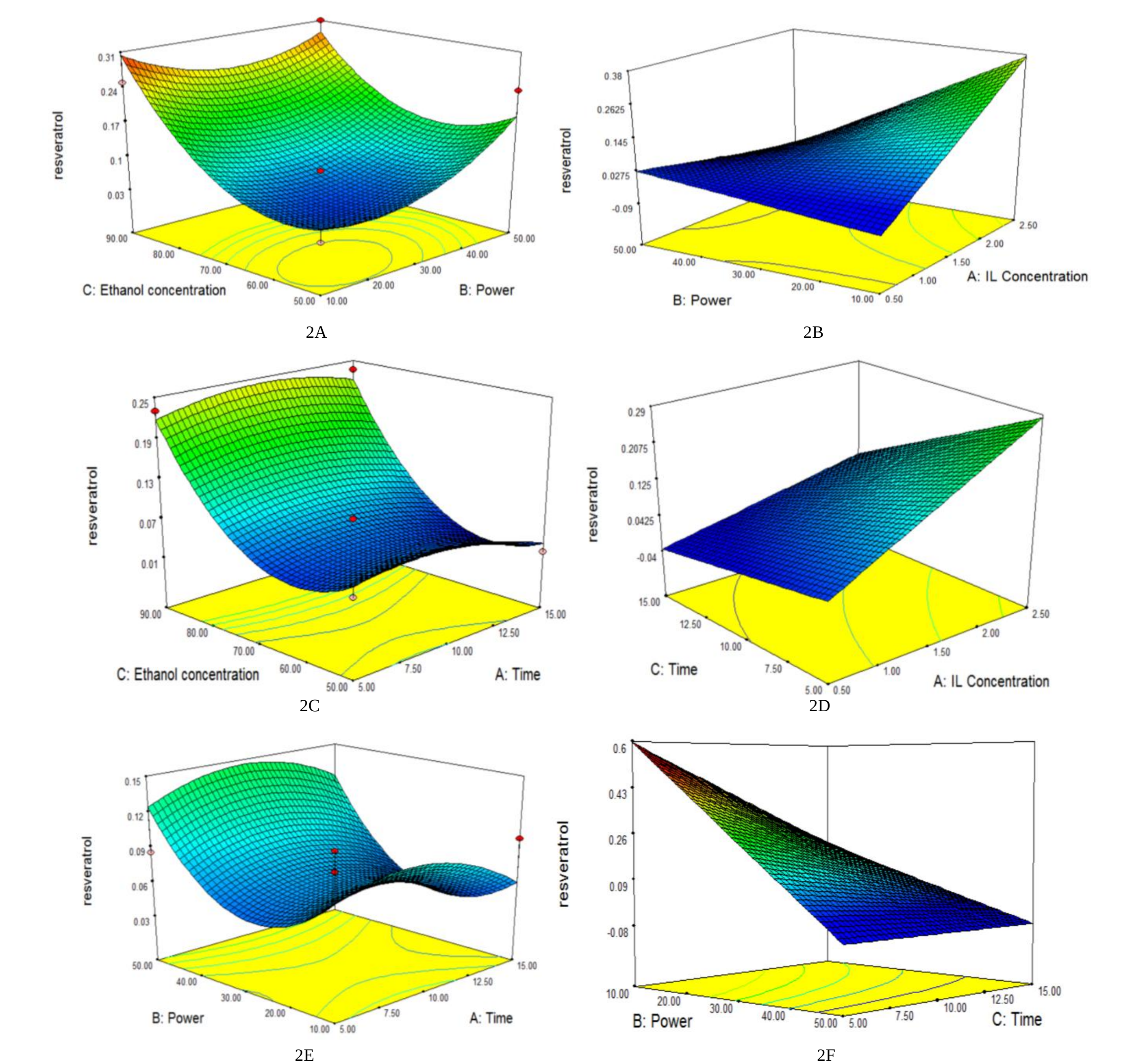


Fig. 1: Response surface interaction of two independent varibles on trans-resveratrol content for MAE-etanol a(a) (c) and (e) and for IL-MAE (b), (d) and (f).

Optimum extraction parameters

Based on the analysis by Design Expert software, there are 13 runs samples that should be analyzed in some condition, and the following is the yield of resveratrol obtained from MAE with ethanol as a result of analysis of samples as listed in Table 1. The highest *trans*-resveratrol content was shown in run 6 with 90% ethanol concentration, 50% microwave power, and 10 minutes extraction time. The experiment value was reached 0.31 mg/g, and that was closed enough to predicted value analyzed by the software which is 0.28 mg/g. The 13 runs of 3 factorial 3 level different experimental IL-MAE conditions were studied, and the result for *trans*-resveratrol yield was shown in Table 2.

The highest value of *trans*-resveratrol content was shown in run six with 2.5 M [Bmim] Br solution, 10% microwave power, and 10 min extraction time. The experiment value was 0.52 mg/g. It was slightly higher compared to the predicted value by Design Expert software was 0.42 mg/g. The run five also showed the high value of *trans*-resveratrol, 0.40 mg/g, with the predicted value was 0.37 mg/g.

Based on the research, results of the optimization of the MAE acquired response surface methodology (RSM) on levels of resveratrol in the extract was 0.31 mg/g dry weight. Compared to the resveratrol obtained in grape seeds (*Vitis vinifera*) with conventional extraction methods for about 19 h only reach 0.107

mg/g (Casazza *et al*., 2010), and the skin can reach 0.169 mg/g by solid-liquid extraction for 48 h (Vincenzi *et al*., 2013) and also compared to *trans*-resveratrol yield of melinjo seed by HRE method which is only 0.093 mg/g. MAE-ethanol method is an entirely comparable method to obtained higher yield of *trans*-resveratrol, because of dielectric properties of the solvent towards microwave heating play a major role in microwave extraction. The high dielectric constant of polar solvent will absorb microwave energy better, so the polar solvent is better used in MAE compared to nonpolar solvent. Thus the use of ethanol is the right choice because in addition to ethanol is a polar solvent, resveratrol also well dissolved in ethanol (Wang and Weller, 2006).

In this research, the MAE extraction yield between ethanol and ionic liquid [Bmim]Br is also compared, and the research showed that IL-MAE gave higher extraction outcome compared to MAE with 90% ethanol at the same parameter. Ionic liquid [Bmim]Br was suited to extract *trans*-resveratrol efficiently because of its strong interaction with *trans*-resveratrol. These multi-interactions of ionic charge and a hydrogen bond between the ionic component and *trans*-resveratrol resulting in the higher dissolution of *trans*-resveratrol (Du *et al*., 2007). By increasing the concentration of the IL solution, it's also increasing the extraction yield. The optimum level of [Bmim]Br solution was 2.5 M, that was suitable concentration to make ionic liquid rupture and penetrate through cell membrane structure, and the target compound in the cell membrane can be dissolved into the solvent. But there is also the disadvantage of concentration enhancement. When the concentration of [Bmim]Br solution over enhances, it also increased the viscosity of the solution. The more viscous of the solution then the more delicate ionic liquid to penetrate the cell membrane because it worsens the diffusion ability. Thus, the efficiency extraction was affected, and the extraction rate would be decreased (Zhang *et al*., 2011)

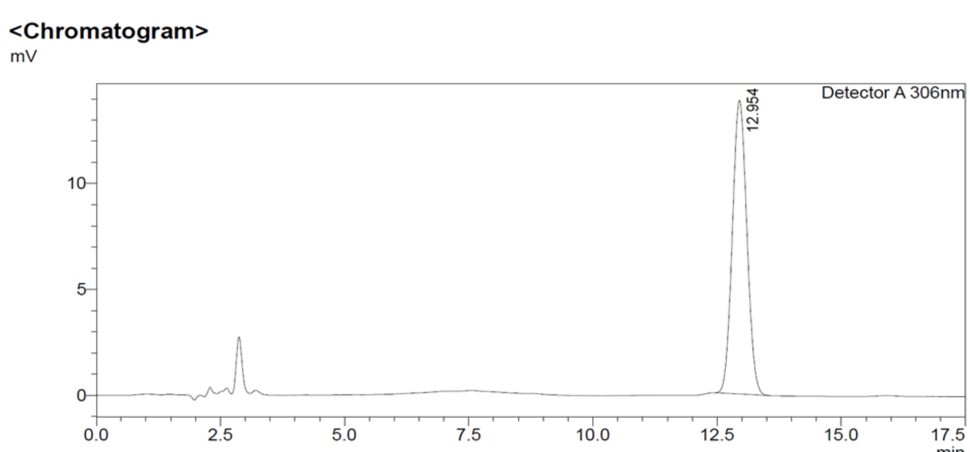
Comparison of MAE method by ethanol and IL

The first thing to be expected with HPLC analysis method on the experiment was to obtain high separation efficiency and peak resolution of the target compound. So then the quantitative analysis of *trans*-resveratrol of the *Gnetum gnemon* L. extract at optimized condition was carried out using high performance liquid chromatography (HPLC).

Resveratrol in samples was identified by their corresponding chromatograms and retention time in comparison with that of the authentic resveratrol standard compound. With some modification on the method (Rabesiaka *et al*., 2011), the retention time of *trans*-resveratrol from MAE method was 13 min and analysis time was 16 min, but it was different retention time of *trans*-resveratrol from HRE which was in 8.5 min. Chromatogram of each extract was shown in Fig. 2.

Various techniques, cost, and complexity have been done to be applied to extract the active components of the plant. Ideally, the extraction method selected must a complete to produce to the maximum desired component of secondary metabolites, with fixed should give priority to the principle is simple, fast, safe, economical, environmentally friendly, and reproducible. HRE is known to be the most suited method that fulfills the requirement, but high-tech extraction methods have proven to be more efficient and economical for extracting the active components of the plant by using microwave-assisted extraction (Ahmad *et al*., 2017).

Ethanol extraction of melinjo seed has also been conducted using heat reflux extraction (HRE), and the result was compared to the *trans*-resveratrol yield obtained by ethanol-MAE and IL-MAE. The *trans*-resveratrol yield of HRE method was 0.093 mg/g, and 0.31 mg/g was obtained by ethanol MAE and 0.52 mg/g by IL-MAE. The MAE method showed the higher extraction yield than HRE. Microwave-assisted extraction (MAE) was selected to be the methods of extraction for some advantages that microwave extraction can decrease the irradiation time with increasing pressure and temperature inside the vessel within a short time, so it raised the boiling point of the solvent used. The use of a volatile solvent can be employed because the loss of it can be avoided, so less solvent is required (Mandal *et al*., 2007). MAE also can improve the extraction yield and product quality, because materials can be rapidly heated, and often processed at lower temperatures. So that why MAE method is suitable for substance that can be degraded by heat like *trans*-resveratrol (Liazid *et al*., 2007). In this research, IL-MAE was showed to be more effective solvent to extract *trans*-resveratrol compared to ethanol. Therefore, IL-MAE could be suggested as an alternative method for the extraction of the bioactive compound from the plant, because it showed comparable result to the existing and conventional method.



3A

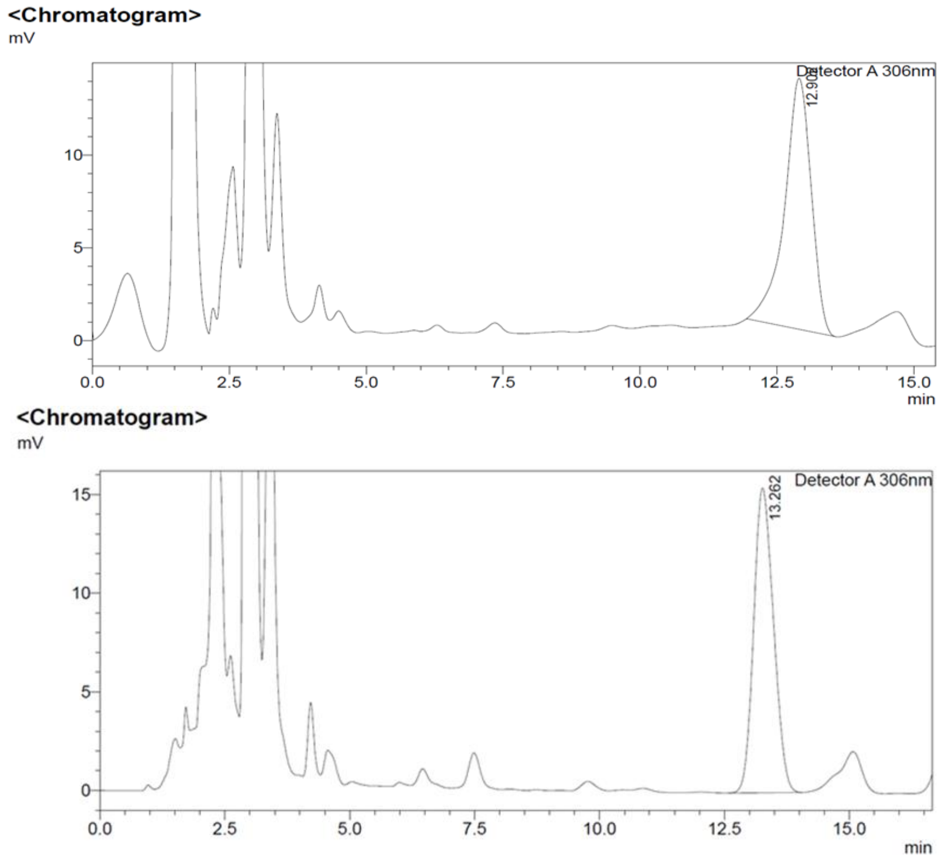


Fig. 2: HPLC chromatograms of standard trans-resveratrol 1mg/L (3A), extract from melinjo seeds by ethanol-MAE (3b), and extract of melinjo seeds by IL-MAE [Bmim] Br (3c).

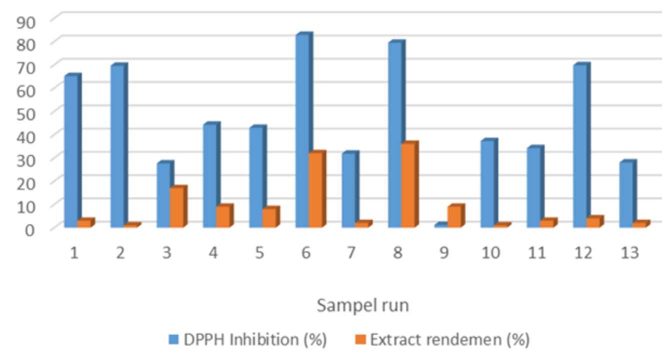


Fig. 3: DPPH inhibition compared to extract yield.

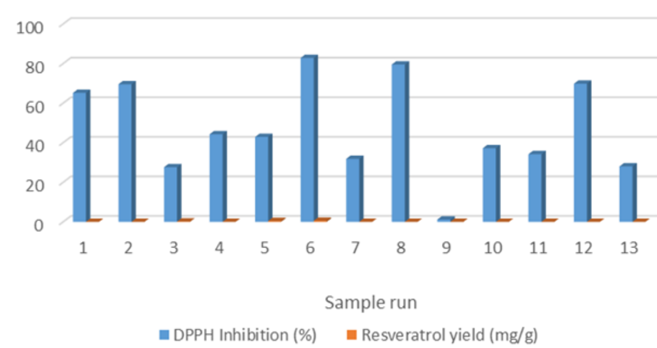


Fig. 4: DPPH inhibition compared to trans-resveratrol yield.

Radical scavenging activity of IL-MAE melinjo seed extract

As mentioned before that *trans*-resveratrol had a good effect as an antioxidant. The in vitro methods widely used for achieving the antioxidant activity is DPPH (1,1-diphenyl-2-picrylhydrazyl) scavenging activity. DPPH scavenging assay is a rapid, simple, and inexpensive colorimetric experiment which determines the percent inhibition of antioxidants. DPPH radical is usually used as a substrate to evaluate antioxidant effect; it is a stable free radical that can receive electrons and hydrogen radicals to become stable molecules. DPPH method was used for the quantification of total antioxidant activity which involves the reactions of the reactive oxygen species with some reagents and formed the complex which is Vis spectrometrically detected at 517 nm wavelength. This research evaluates the antioxidant activity of IL-MAE melinjo seed extract. From the optimization data of IL-MAE method extraction, the highest DPPH inhibition value is run 6 and run 8, which is in line with the *trans*-resveratrol concentration obtained and also rendemen of extract as showed in Figure 3 and Figure 4. The maximum DPPH inhibition was 82.82%. When compared to DPPH activity of melinjo seed extract from conventional extraction, which inhibits only 5.96%, then IL-MAE melinjo seed extract was more potential antioxidant.

CONCLUSION

The IL-mae method with [Bmim]Br solution is suitable for the extraction of *trans*-resveratrol of defatted melinjo seed. The optimum condition of the IL-MAE method was 2.5 mol/L ionic liquid [Bmim]Br concentration; 10% of microwave power and irradiation time within 10 min. The optimal value of *trans*-resveratrol was 0.52 mg/g dry melinjo seed powder. Followed by the DPPH inhibition of extract was 82.82%.

ACKNOWLEDGMENT

Financial support and sponsorship: This work was financially supported by Direktorat Riset dan Pengabdian Masyarakat, Universitas Indonesia Via Hibah PITA 2016.

Conflict of Interests: There are no conflicts of interest.

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How to cite this article:

Rachmawati M, Ayuningtyas IN, Sutriyo S, Mun'im A. Comparison of Ionic Liquid-Microwave-Assisted Extraction and MAE of Resveratrol from Melinjo (*Gnetum gnemon*L.) Seeds. J App Pharm Sci, 2017; 7 (10): 023-029.