

Optimization of ionic liquid-microwave assisted extraction method of Mahkota Dewa (*Phaleria macrocarpa* (Scheff.) Boerl.) fruit pulp

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ABSTRACT

Mahkota dewa fruit pulp (*Phaleria macrocarpa*, PMp) is often used as a medicinal raw material in Indonesia. The texture of the *P. macrocarpa* fruit is hard due to high lignin and cellulose contents and it often inhibits an extraction process of secondary metabolism. This study is conducted to get optimum extraction condition by using the ionic liquid-microwave assisted extraction (IL-MAE) method, assessing the effect of pretreatment with urea and the antioxidant activity of PMp. Solvent [BMIM]BF₄ has been chosen for extraction by varying three parameters: solvent concentration, extraction time, and solvent-sample ratio. The optimum condition was determined based on total phenolic content (TPC; milligram equivalent to quercetin as reference), antioxidant activity assay has been carried out using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) method, and selectivity to extract polar compound was carried out using High-Performance Liquid Chromatography (HPLC) method. The optimum extraction condition has been achieved at run 11 with the condition: 10% microwave power, using [BMIM]BF₄ (2.5 M) as a solvent, using 0.01 M KH₂PO₄ as a salt solution, 2.5 minutes extraction time, solvent: sample ratio (17.5: 1), resulting TPC value of 191.72 ± 1.27 mgGAE/g powder, and DPPH radical-scavenging activity of 12.1 ± 0.003%. The IL-MAE method can extract the marker of phenolic compounds (quercetin, mahkocide, benzophenone, and mangiferin) and showed selectivity in extracting polar compound than conventional methods. Pretreatment using 8% urea for 12 hours produced no significant difference in TPC values from the IL-MAE method at optimum conditions. The IL-MAE method gives the highest TPC and superior antioxidant activity in PMp extraction.

INTRODUCTION

Phaleria macrocarpa (PMp), locally known as Mahkota dewa, is an endemic plant of Indonesia which has been used for a long time as a medicine to cure a variety of diseases such as cancer, liver, heart, diabetes, arthritis, kidney, stroke, and hypertension (Daud *et al.*, 2016; Hendra *et al.*, 2011). The fruit pulp of *P. macrocarpa* (PMp) contains a variety of secondary metabolites. Various previous studies have been conducted to investigate and prove its benefits as a preventive therapy in cancer and hypertension. From these studies, it is known that the compound group which plays an important role is the phenolic group compound. The phenolic compound is the highest content

consisting of mahkocide, phalerin, benzophenone, mangiferin, and kaempferol-3-O-β-glycoside compounds (Oshimi *et al.*, 2008; Yanti *et al.*, 2014; Zhang *et al.*, 2012). The pulp of PMp is known to be fibrous and watery (Figure 1); the main fibrous components consist of cellulose, hemicellulose, lignin, β-glucan, gums, pectin, and hydrocolloid (Lay *et al.*, 2014). The high fiber content makes the extraction process of beneficial compounds more difficult and it requires special treatment.

Some of the methods have been conducted in PMp extraction including maceration, soxhlet, reflux, and supercritical fluid extraction (Alara and Olalere, 2016). The extraction process using microwaves is also being considered. Microwave-assisted extraction (MAE) involves interference at the internal structure of cells. The exposure of microwave creates heat and high temperature inside of the cell matrix, resulting in the cell friction and the release of active constituents (Chen *et al.*, 2017; Ekezie *et al.*, 2017; Delazar *et al.*, 2012). By using this technique, the beneficial compounds in the plant will be extracted easily.

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Figure 1. Fruit of Mahkota dewa (*Phaleria macrocarpa* (Scheff.) Boerl.).

In line with the development of the extraction method, the usages of ecofriendly solvents are also being developed. Ionic liquid (IL) is one of the common solvents explored. IL is an organic salt in the liquid form consisting of organic cations and organic or inorganic anions. The combination of MAE with IL is often used as an alternative extraction technique for extracting active substances of medicinal plants; this method becomes more popular as IL-MAE (Chen *et al.*, 2017).

Another strategy in compound extraction from plants is reducing the lignin and hemicellulose contents, confounding the structure of plant cell walls for increasing solvent access in the cell matrix (Sun *et al.*, 2016). This strategy is known as pretreatment. Pretreatment was commonly being used with chemicals, such as urea. In a previous study, it was mentioned that adding the urea with alkaline solutions in pretreatment can increase the solubility of cellulose (Isobe *et al.*, 2013; Xiong *et al.*, 2013). Adding urea as a base added before extraction is believed to increase the extraction results.

This research was carried out to obtain the IL-MAE optimum condition compared to the other conventional extraction techniques, such as reflux, soxhlet, and extraction with urea pretreatment. The results of the study are expected to be used as preliminary data in determining the suitable extraction methods to produce optimum extracts in terms of extraction efficiency which is measured through TPC and antioxidant activity of the sample.

MATERIALS AND METHODS

Plant material

The dried fruit pulp of Mahkota dewa (*P. macrocarpa* (Scheff.) Boerl) has been obtained from Purworejo, Central Java, Indonesia, and has been identified by Lembaga Ilmu Pengetahuan

Indonesia (LIPI), Pusat Penelitian Biologi, Cibinong, Central Java, with voucher code 817.

Chemicals

[BMIM]BF₄ (Shanghai Cheng Jie Chemical Co., China), Na₂CO₃, KH₂PO₄, NaCl (Brataco, Indonesia), urea (Harum Chemistry), ethyl acetate proanalysis, methanol proanalysis, methanol HPLC grade, distilled water (Merck), gallic acid reference with purity >98.5% (Sigma-Aldrich Co., USA), sodium carbonate (Sigma-Aldrich Co., USA), Folin–Ciocalteu reagent (Sigma-Aldrich Co., USA), BHT, and DPPH reagent (Sigma-Aldrich Co., USA) were used.

Instruments

Design-Expert™ version 10.0.0 data processor, microwave (Modena) modified for MAE, high-performance liquid chromatography (Shimadzu LC-20AT), 0.45 mm (Agilent) micropore filter, UV-Vis detector (Shimadzu SPD-20 A), microsyringe 50 µl (Hamilton), C18 column (ZORBAX Eclipse), microplate 96 flat bottom (Thermo Scientific), microplate reader (Versa Max), centrifugator (Labsco), and vortex (WiseMix) were used.

Soxhlet extraction

Dried and pulverized fruit pulp (20 g) were extracted in 70% ethanol for 6 hours using a soxhlet apparatus. The resulting mixture was allowed to cool overnight to yield the optimum content of phenolic compounds. The extract was dried with a rotary vacuum evaporator and then in a vacuum oven at 40°C. The TPC was measured using a microplate reader at 750 nm using a method previously conducted by Bobo-Garcia (2015).

Reflux extraction

Similar to the soxhlet extraction, 20 g of the sample was extracted in 200 ml of 70% ethanol for 2 hours at 80°C using a reflux apparatus. The resulting mixture was evaporated under vacuum at 50°C and subsequently dried at 40°C in a vacuum oven to obtain the crude extract. TPC was measured as described in the previous sections.

Determination of salt in Aqueous Biphasic System (ABS)

1 g PMp powder was mixed with 20 ml of 0.5 M [BMIM] BF₄ solution for 5 minutes and was centrifuged at 3,000 rpm for 15 minutes. Supernatant was filtered and partitioned with ethyl acetate and added with 0.01 M Na₂CO₃, KH₂PO₄, or NaCl with a molar ratio of 1:1 v/v. The solution was mixed and centrifuged at 3,000 rpm for 10 minutes. The ethyl acetate phase was taken and was evaporated using a drying oven at 50°C (Ayuningtyas *et al.*, 2017). TPC was measured using a microplate reader at 750 nm using a method previously conducted by Bobo-Garcia (2015). The yield was calculated. An extract that shows the highest yield and TPC was further selected for optimization with response surface methodology.

IL-MAE extraction

Experimental design

The optimization of extraction conditions was carried out using Design-Expert® software version 10.0.0 by selecting the Box–Behnken method. Three extraction parameters (concentration (M), extraction time (minutes), and ratio solvent: sample) were determined and showed in Table 1. From the set parameter, 17 run extraction designs have been obtained (Table 2).

IL-MAE extraction

Extraction was carried out in 17 conditions (runs) as showed in Table 2. 1 g of PMp powder was extracted in the microwave for 5 minutes at 10% power and under the conditions (parameters) as specified in Table 2 for each run. The extract obtained was fractionated using ethyl acetate and selected salt

solution (0.01 M KH_2PO_4) which was previously achieved at the determination of salt in the ABS step. The ethyl acetate fraction was collected and dried in a drying oven at 50°C for 2 days. The yield and TPC were calculated.

Antioxidant activity assay

Antioxidant activity assay was performed using a microplate reader conducted by Bobo-Garcia, 2015 method. The absorbance was measured at 517 nm. Antioxidant activity was determined through the percentage of DPPH radical-scavenging activity using the following equation:

$$A = \text{absorbance.}$$

Chromatogram profile analysis

Chromatogram profile investigation of PMp extract was carried out by the HPLC method according to Winarno *et al.* (2010) using column (C-18), mobile phase (acetonitrile:water for injection:acetic acid (89:10:1)), flow rate (1 ml/minute), detector (UV, at 254 nm for quercetin, 280 nm for benzophenone and mahkoxide, and 288 nm for mangiferin), and injection volume (20 μl).

Pretreatment using urea

Pretreatment was carried out using 1 g PMp and 8% urea (w/w gram of PMp powder). The volume was adjusted 10 ml with

demineralized water (Jin *et al.*, 2007). The immersion with urea was carried out for 12 hours based on a preliminary experiment. After pretreatment, the sample was extracted with $[\text{BMIM}]\text{BF}_4$ 0.5 M for 5 minutes and was partitioned with KH_2PO_4 (Ayuningtyas *et al.*, 2017). TPC and antioxidant activity were determined (Bobo-Garcia, 2015).

RESULTS AND DISCUSSION

Ionic liquids are solvents that should not be consumed; therefore, before the extract can be consumed, the extract must be partitioned first from the ionic liquid solvent to induce the salting-out process during partition. The process of extract partition from solvent IL is called an ABS, also known as the aqueous two-phase system. ABS is formed from the contact of two immiscible solvents. The principle is the selective distribution of compounds between two phases (Shukla *et al.*, 2017). ABS consists of polymer combinations: salt polymer, salt in water solutions, and solvents which immiscible with water, such as ethyl acetate (Wu *et al.*, 2016). The ABS usage in the separation of compounds from ionic liquids was first performed by using $[\text{BMIM}]\text{Cl}$ as ionic liquids and K_3PO_4 as inorganic salt (Gutowski *et al.*, 2013). In this research, KH_2PO_4 salt produces the highest TPC (71.69 ± 1.17 mg GAE/g PMp powder) compared to carbonate and chloride salt (Figure 2). This finding is in line with previous research with different samples which showed that KH_2PO_4 salt can be used for liquid partitions because it will induce salting out immediately after application. KH_2PO_4 salt is easy to form ABS with hydrophobic ionic liquids and induce the formation of an Aqueous Biphasic System (Mourao *et al.*, 2012).

The yield of IL-MAE extraction was directly proportional to TPC. Run 11 showed the highest yield and TPC, while run 8 has the lowest yield and TPC (Table 2). Run 11 yielded 684.3 mg/g powder containing 191.72 ± 1.27 mg GAE/g powder.

Table 1. IL-MAE parameters of optimization.

No.	Factors	Level		
		-1	0	+1
1.	IL concentration (M)	0.5	1.0	1.5
2.	Solvent: sample ratio	12.5	15	17.5
3.	Extraction time (min)	1.5	2.5	3.5

Table 2. TPC of several conditions.

Run	Concentration (M)	Extraction time (minutes)	Ratio solvent: sample (ml/g)	Total yield (mg/g powder)	TPC (mg GAE/g powder)
1	1	1.5	12.5	171.5	67.37 ± 0.35
2	1	2.5	15	229	92.69 ± 1.30
3	1	2.5	15	247	92.96 ± 0.53
4	1	2.5	15	256.4	93.18 ± 1.18
5	0.5	2.5	17.5	104.3	52.90 ± 1.04
6	1	2.5	15	216.2	90.30 ± 1.19
7	1	2.5	15	328.5	92.47 ± 1.62
8	0.5	2.5	12.5	42.4	34.10 ± 0.20
9	1	1.5	17.5	395.2	146.91 ± 1.64
10	1.5	1.5	15	554.8	180.18 ± 1.67
11	1.5	2.5	17.5	684.3	191.72 ± 1.27
12	1.5	3.5	15	570	167.88 ± 2.09
13	1	3.5	17.5	374.2	137.32 ± 2.67
14	0.5	1.5	15	85.3	40.94 ± 0.23
15	1.5	2.5	12.5	342	157.79 ± 2.29
16	0.5	3.5	15	73.7	46.85 ± 0.23
17	1	3.5	12.5	178.8	74.09 ± 0.91

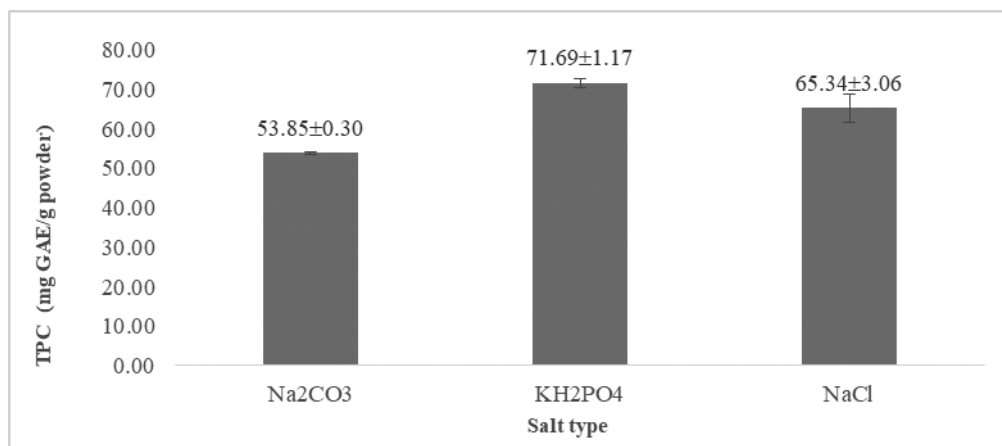


Figure 2. TPC in three types of salt.

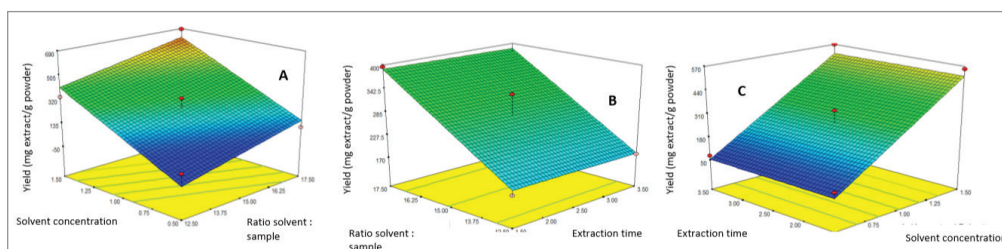


Figure 3. Surface response graph showed the yield (mg/g powder) of two parameters. (a) Solvent: sample ratio and solvent concentration. (b) Solvent: sample ratio and extraction time. (c) Solvent concentration and extraction time.

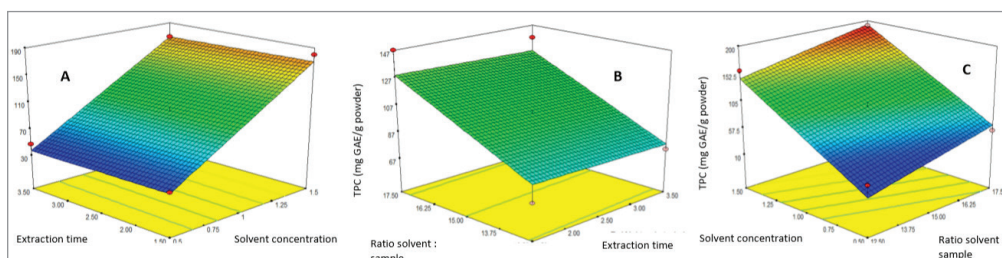


Figure 4. Surface response graph showed the TPC of two parameters. (a) Solvent concentration and extraction time. (b) Solvent: sample ratio and time. (c) Solvent: sample ratio and solvent concentration.

The surface response graph was demonstrated in Figures 3 and 4 (optimum conditions are shown in red-yellow on the graph). In the yield and TPC analysis, significant parameters that affect yield and TPC are solvent concentration and solvent-sample ratio because their “*p*-value” is less than 0.0001, while the extraction time is not significant because the value of “*p*” is more than 0.1.

TPC resulting from IL-MAE in optimum conditions (run 11) was compared with TPC resulting from reflux and soxhlet extraction. IL-MAE produced a higher TPC than TPC in conventional methods (Figure 5). This finding indicates that the optimization of IL-MAE extraction has succeeded in more increasing TPC almost five times than conventional extraction. In the previous studies, *1-Butyl-3-methylimidazolium tetrafluoroborate* ([BMIM] BF₄) was used to extract phenolics, flavonoids, and phenolic alkaloids using Ultrasonic Assisted Extraction, Microwave-Assisted Extraction, and conventional

extraction method (Tang *et al.*, 2012). Lu *et al.* (2008) found that [BMIM]BF₄ is the most efficient and selective solvent in extracting phenolic compounds. The separation mechanism is based on the hydrogen-bonding interaction between IL’s anion and the –OH group of phenolic compounds (Lu *et al.*, 2008).

The IL-MAE efficiency for extracting PMp containing lignin and cellulose has been strengthened by the results of TPC and antioxidant activity comparison in extraction using 8% urea. The results obtained from TPC and antioxidant activity in samples given urea (pretreatment) are higher than nonpretreatment extraction in optimum condition (Table 4). This result is consistent with the literature which stated that urea addition can increase cellulose solubility and yield of extraction (Xiong *et al.*, 2014). Urea is an additional chemical of the cellulose dissolution process in alkalic conditions. The addition of urea increases the cellulose dissolved fraction in

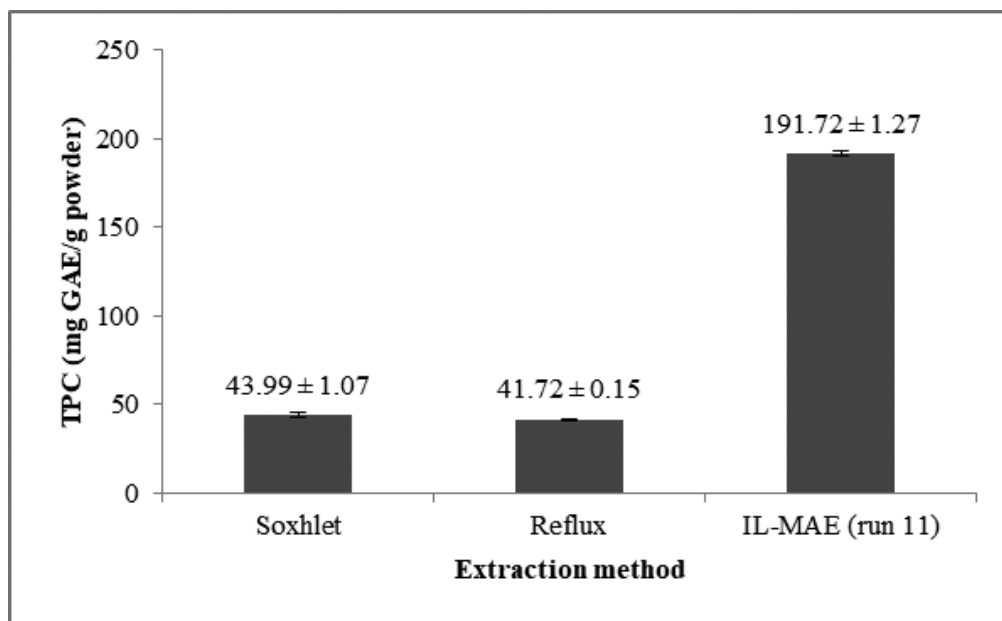


Figure 5. TPC in different methods: soxhlet, reflux, and IL.

Table 3. Chromatogram profile analysis results.

Wavelength (λ)		254 nm		280 nm				288 nm					
Peak		tR	Area	tR ₁	Area ₁	tR ₂	Area ₂	tR ₁	Area ₁	tR ₂	Area ₂	tR ₃	Area ₃
Quercetin	Reff	5.962	1557										
	IL-MAE	6.144	20858										
	Reflux	6.006	214996										
	Soxhlet	6.096	183502										
Benzophenone	Reff			8.171	3863	11.338	1008						
Mahkoside	Reff			8.134	540	11.286	745						
	IL-MAE			8.195	9250	11.374	1338						
	Reflux			8.131	12842	11.305	6583						
	Soxhlet			8.159	1573	11.382	4711						
Mangiferin	Reff							9.806	1588	10.714	1391	11.168	1558
	IL-MAE							9.76	1264	10.832	1516	none	none
	Reflux							none	None	10.744	4198	11.237	2145
	Soxhlet							9.857	1390	None	None	11.137	6523

*Reff = reference.

tR: time retention in minutes.

Table 4. The effect of pretreatment on TPC and antioxidant activity.

Sample	TPC (mg GAE/g powder)	DPPH-scavenging activity (%)
Pretreatment	124.47 ± 1.05	20.26 ± 0.002
Nonpretreatment	191.72 ± 1.27	12.1 ± 0.003

solvents by 1.5–2.5 times and the solution thermal stability (Isobe *et al.*, 2013). However, the TPC value in pretreatment and nonpretreatment is not much different. Pretreatment by using urea takes 12 hours, while IL-MAE only takes 2.5 minutes in processing time. By considering the time efficiency, extraction using IL-MAE at optimum conditions produces superior results among all the methods in this study.

IL-MAE efficiency has been qualitatively compared with conventional extraction methods through chromatogram profile in HPLC analysis. The analysis was conducted using acetonitrile: water for injection: acetic acid (89:10:1) as mobile phase, considering the polarity of polyphenolic marker compounds (quercetin, benzophenone, mahkoside, and mangiferin). Figure 6 showed quercetin in minute 5.96, benzophenone, mahkoside in minutes 8 and 11, and mangiferin in minute 9.80; 10.71; and 11.17. Chromatogram profile extract from IL-MAE showed more selective results than reflux and soxhlet; there is no peak detected in minutes 12–14 (at 254 nm), in minutes 10–11 (at 280 nm), and in minutes 8–9 (at 288 nm) compared to reflux and soxhlet method (Figure 6).

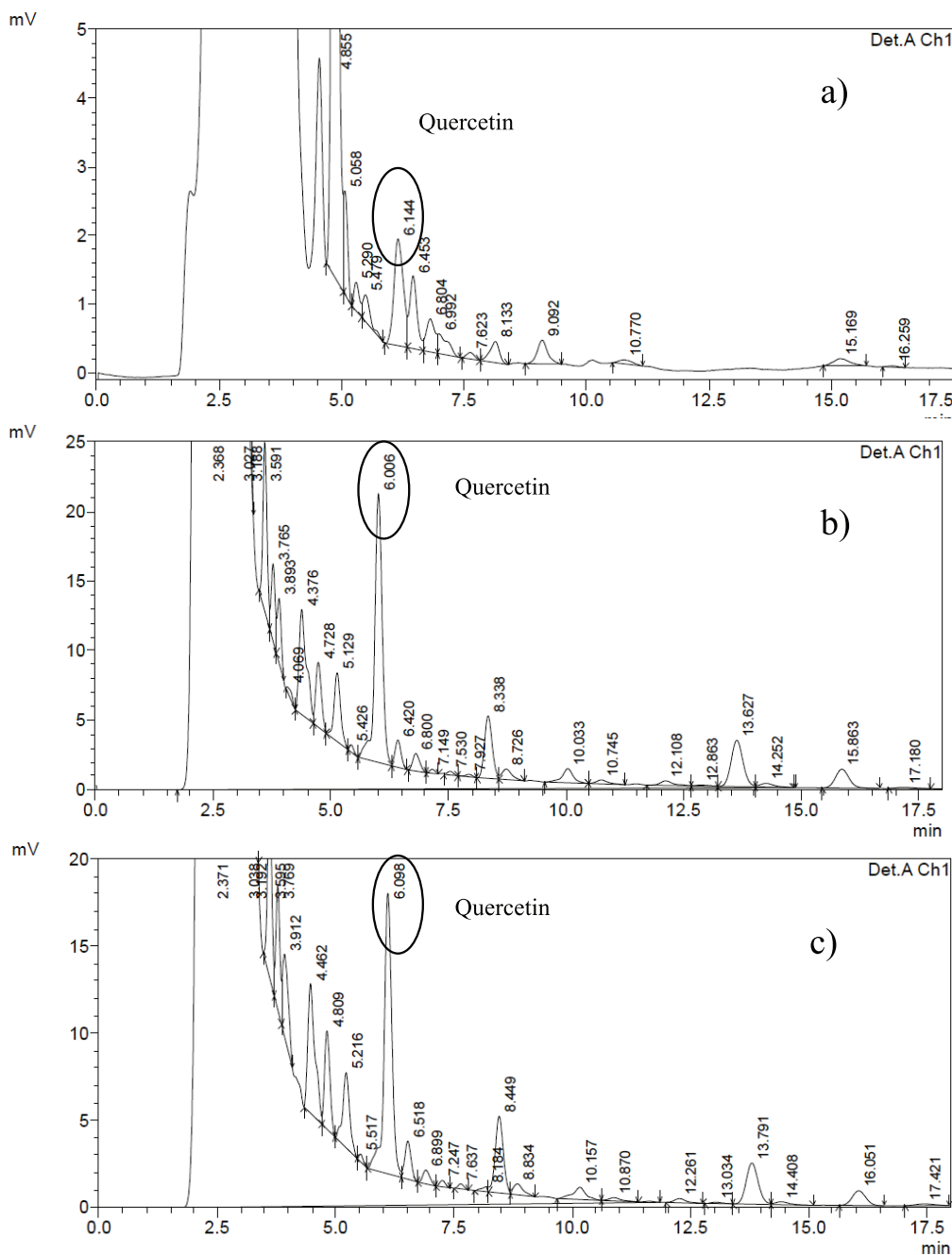


Figure 6. Chromatogram profile: (a) IL-MAE, (b) reflux, and (c) soxhlet (at 254 nm).

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

ETHICAL APPROVALS

This study does not involve the use of animals or human subjects.

ABBREVIATIONS

DPPH: 1,1-diphenyl-2-picrylhydrazyl, GAE: gallic acid equivalent, IL: ionic liquid, IL-MAE: ionic liquid-microwave assisted extraction, PMp: *Phaleria macrocarpa* fruit pulp, TPC: total phenolic content.

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