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Ionic Liquid-Based Microwave-Assisted Extraction: Fast and Green Extraction Method of Secondary Metabolites on Medicinal Plant

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ABSTRACT

Background: Ionic liquid-based microwave-assisted extraction (IL-MAE) is one of the nonconventional extraction methods that has been developed and applied in recent years. Some studies have reported the success of this approach for extracting the target compound (secondary metabolites) from medicinal plants optimally. **Objective:** This review paper aimed to provide detail information about the application of the IL-MAE method as a fast and green extraction of a secondary metabolite from the medicinal plant. **Materials and Methods:** The literature published on IL-MAE was searched and collected using online resources from the electronic databases including Google Scholar, DOAJ, PubMed, ScienceDirect, and Scopus. **Results:** This review highlights the role of IL as a green solvent and the basic principles and mechanisms of MAE and its utilization of natural product extraction. **The application of the IL-MAE method to extract secondary metabolite (particularly the targeted compound) from a medicinal plant, and a brief extraction mechanism of IL-MAE using Fourier-transform infrared spectroscopy and scanning electron microscopy.** **Conclusion:** The application of IL-MAE method has successfully performed to extract the targeted secondary metabolite from a natural product, where the extraction process to be rapid, efficient, and green.

Key words: Ionic liquid-based microwave-assisted extraction, ionic liquids, medicinal plant, microwave-assisted extraction, secondary metabolite

INTRODUCTION

Exploration of the active constituents of natural products has been done for a long time. However, the resultant products are still relatively small that can be used commercially. Scientific research on natural products (especially traditional medicine), ranging from the search for raw materials, production processes, to the test of efficacy and toxicity has been done so far. Problems in the development of raw materials from nature are still constrained by different quality depending on various conditions.

The natural products (plants, animals, and microorganisms) are a sustainable source in nature that is known to be beneficial to humans for thousands of years. The diversity of species from natural products is still a primary source of ideas for the development of new drugs, functional food, and food additives.^[1] In general, the active compound of the natural product is a secondary metabolite produced through biological pathways of various biosynthetic pathways and is obtained using an appropriate extraction procedure.^[2,3] The active constituents of natural products can be extracted by multiple conventional and nonconventional extraction techniques.^[4,5] Most of these methods based on exploration of different solvent strengths.

Application of green chemistry principles to explore the potential of active constituents from natural products continues to rise, in this case, the use of liquid as a solvent.^[6] Ionic liquids (ILs) were selected because they are nonflammable, stable at high temperature, nonvolatile, nontoxic, and have the flexibility to adjust the physicochemical properties of the target compound.^[7] Furthermore, economic and environmental impact standpoint should even be considered in the selection of solvents.^[8]

IL-based microwave-assisted extraction (IL-MAE) is one of the non-conventional methods of extraction that has been developed and applied in recent years. The principle of using the IL-MAE is the same as the principle of the MAE method, only differing in the principle and type of solvent used. Success in applying this technique to obtain the optimal of target constituents has been widely reported including resveratrol

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1 extraction of *Polygonum cuspidatum* Sieb.et.Zucc.,^[9] phenolic alkaloid
2 extraction of *Nelumbo nucifera* Gaertn.,^[10] Essential oils extraction of
3 some plant, namely *Illicium verum*, *Cuminum cyminum*,^[11] *Schisandra*
4 *chinensis*,^[12] *Cinnamomum* spp.,^[13] quercetin and kaempferol extraction
5 from *Toona sinensis* and *Rosa sinensis*,^[14] flavonoid extraction from
6 *Cajanus cajan* and *Scutellaria baicalensis*,^[15,16] secondary metabolite
7 and polyphenolic extraction from *Peperomia pellucida* (L) Kunth,^[17,18]
8 and so on. This review aimed to provide detail information about the
9 application of the IL-MAE method as a fast and green extraction of a
10 secondary metabolite from the herbal plant.

11 MATERIALS AND METHODS

12 This article reviews about an ionic IL-MAE method for secondary
13 metabolite extraction on the herbal plant from extensive literature.
14 The literature was searched between January and October 2017 from
15 the electronic databases including Google Scholar, DOAJ, PubMed,
16 ScienceDirect, and Scopus.

17 RESULTS AND DISCUSSION

18 Ionic liquid as a green solvent for extraction

19 Knowledge of the solubility properties of the target constituents in the
20 natural products is essential to know for the extraction and separation
21 process to maximally succeed. Some potential components of natural
22 products (especially medicinal plant) have low solubility in water then
23 usually used organic solvents such as alcohols, ethers, ethyl acetate,
24 alkanes, chloroalkanes, and other organic solvents. However, the
25 selection of such solvents can be selected if the targeted or already
26 literature constituents are known. If the information is not available,
27 then it should follow the principle of "like dissolves like."^[19]

28 The widely accepted and understood polarity concept based on the
29 polarity definition is the number of all intermolecular (specific and
30 nonspecific interactions) between the solvent and the potential of the
31 solute, this interaction produces a chemical reaction.^[20] It can be regarded
32 as both a physical and chemical phenomenon consisting of Coulomb
33 interaction, dipole-dipole interactions, hydrogen bond interactions,
34 and acid-base donor-acceptor interactions. Associated with the polarity
35 of ILs depends on the nature of the components, usually in the range
36 of dipolar nonhydrogen-bond-donation solvents (DMF, DMSO, and
37 acetonitrile) to polar hydrogen-bond-donation solvents (primary
38 alcohols, water).^[19,20] Furthermore, other significant factors affect such as
39 boiling point and melting point, density, viscosity, and surface tension of
40 the solvents.^[21] The ILs can be considered as "self-assembly amphiphiles"

1 that form an H-bonded-polymeric network becomes a common
2 structure pattern as a solid and liquid phase.^[22,23]

3 The ILs or room temperature ionic liquid is a promising candidate that
4 can meet the above requirements which consist entirely of stable organic
5 cations and inorganic or organic anions, can be seen in Table 1 which
6 is liquid at room temperature and has unique properties, such as high
7 thermal stability, nonflammability, and low chemical reactivity.^[24-27]
8 Because of these uniqueness that has properties with the viscosity,
9 fine-tunable density, polarity, and miscibility with common organic
10 solvents, which are highly applicable in areas such as analytical
11 chemistry,^[28] catalysts and synthesis,^[29,30] electrochemistry,^[31] and most
12 importantly, ILs can be applied in the separation process (extraction)
13 from natural products.^[27,32-34]

14 The selection of solvents with the approach of the principle of green
15 chemistry in exploring the constituent target and potential of active
16 compound from natural products continue to rise, in this case, the
17 use of ILs as a green solvent.^[6] The ILs can be employed as a solvent
18 because they have the flexibility of ions combinations (cations
19 and anions) to adjust the physicochemical properties of the target
20 constituents and can be considered possible substituents to replace
21 volatile and toxic organic solvents whereas ILs otherwise.^[7,33] Besides to
22 the physicochemical properties of ILs that affect the extraction results,
23 several other considerations regarding the overall process, economic and
24 environmental impacts standpoint should also be considered.^[8,33,35-37]

25 The ILs as a solvents are widely used for extracting secondary metabolite
26 (especially polyphenols and alkaloids) from natural products such as
27 1-butyl-3-methyl imidazolium chloride [BMIM] Cl, 1-butyl-3-methyl
28 imidazolium bromide [BMIM] Br, 1-butyl-3-methyl imidazolium
29 tetrafluoroborate [BMIM] BF₄, 1-butyl-3-methyl imidazolium
30 dihydrogen phosphate [BMIM][H₂SO₄], 1-butyl-3-methyl imidazolium
31 hydrosulfate [BMIM][HSO₄], 1-ethyl-3-methyl imidazolium
32 bromide [EMIM] Br, 1-hexyl-3-methyl imidazolium bromide [HMIM]
33 Br, 1-octyl-3-methyl imidazolium bromide [OMIM] Br, and other
34 types.^[9,16,38-45] In general, the increased ability to attract certain chemical
35 constituents may increase with the increase in hydrophobicity of the
36 solvents used.^[42] Furthermore, the hydrogen bonding capability of ILs is
37 also a factor affecting extraction by considering anions.^[37,46]

38 Toxicity and environmental impact standpoint

39 Since the introduction of green chemistry, especially in this case, the
40 use of ILs as an alternative solvent, at that time also there have been
41 concerns related to toxicity and environmental impact by the originators
42

43 **Table 1:** Some ionic liquids were used as alternative solvent for extracting secondary metabolite from herbal plants

44 ILs	45 Abbreviation	46 Melting point °C	47 Density (g/mL)	48 Viscosity (cP)	49 BM
50 1-ethyl-3-methylimidazolium tetrafluoroborate	(EMIM) (BF ₄)	6	1.248	66	197.8
51 1-ethyl-3-methylimidazolium hexafluorophosphate	(EMIM) (PF ₆)	58-62	1.373	450	256.13
52 1-butyl-3-methylimidazolium tetrafluoroborate	(BMIM) (BF ₄)	-82	1.208	233	225.80
53 1-butyl-3-methylimidazolium hexafluorophosphate	(BMIM) (PF ₆)	10	1.373	400	284.18
54 1-butyl-3-methylimidazolium bromide	(BMIM) Br	60	1.134	Solid	218.9
55 1-butyl-3-methylimidazolium chloride	(BMIM) Cl	89	1.120	Solid	146.50
56 1-butyl-3-methylimidazolium trifluoromethylsulfonate	(BMIM) (CF ₃ SO ₃)	16	1.290	90	260.0
57 1-butyl-3-methylimidazolium bis (trifluoromethylsulfonyl) amide	(BMIM) (NtfO ₂)	-8	1.404	48	433.0
58 1-allyl-3-methylimidazolium tetrafluoroborate	(AMIM) (BF ₄)	-88	1.231	321	240.02
59 1-hexyl-3-methylimidazolium tetrafluoroborate	(HMIM) (BF ₄)	-82	1.075	211	254.08
60 1-butyl-3-methylimidazolium hexafluorophosphate	(HMIM) (PF ₆)	-61	1.304	800	312.0
61 1-octyl-3-methylimidazolium tetrafluoroborate	(OMIM) (BF ₄)	-79	1.11	440	281.2
62 1-octyl-3-methylimidazolium chloride	(OMIM) Cl	0	1.000	16,000	230.50
63 N-methylpyrrolidinium bis (trifluoromethylsulfonyl) amide	(MPPyr) (NtfO ₂)	0	1.44	39	416
64 BAF		-10	0.99	11.5	91
65 N-butylpyrrolidinium bis (trifluoromethylsulfonyl) amide	(BMPPyr) (NtfO ₂)	-50	1.4	71	422

66 ILs=Ionic liquid, BAF=???

of ILs solvent. In the last 10 years, research efforts have focused on increasing biodegradability and examining the toxicity reduction of ILs.^[47] Furthermore, some studies have reported on ILs, where anions have limited effects on the level of ionic biodegradation and the most important component is a cation.^[48] The toxicity of ILs is strongly influenced by its lipophilicity associated with the length of the straight chain alkyl and its branching degree and also is affected by its anionic properties.^[49-51] Peric *et al.* has undertaken toxicity assay studies of the protic ILs (derived from aliphatic and organic acid) and the aprotic ILs (imidazolium and pyridinium) groups to aquatic organisms, as well as tests on the enzyme acetylcholinesterase and mouse leukemia cell (IPC-18), with protic ILs activity >100 mg/L, and aprotic ILs weaker than protic IL.^[52]

The main reason for believing that ILs with nontoxic and nonvolatile properties, make these solvents potential as a green solvent can be an alternative material or substitute for conventional organic solvents. Unfortunately, this green image is misplaced and recently awakened the consciousness of the chemists, especially those who work in the field of green chemistry. It is known that some cations and anions as harmful solvents, however, after the assessments in the known that the risk of harm caused can be reduced by combining an individual cation and anion into an IL solvent.^[47] On the other hand, combining different functional groups makes it complicated to investigate toxicity because it has functional groups that potentially cytotoxic. Although ILs may help in reducing the risk of air pollution, however, its release to the aquatic environment can cause severe water contamination due to its potential toxicity and its uncontrollable biodegradability.^[53] It has a relatively stable form of an ILs so that it can cause accumulation in the aquatic environment. Related environmental impacts and toxicities have been described in more detail in some literature.^[47,53,54] However, with nonflammable properties and reproducible, so that the utilization of ILs as a green solvent becomes more economical and eco-friendly.

Microwave-assisted extraction

The development of nonconventional extraction methods has been widely practiced. The MAE method is one of the nonconventional methods that is quite easy to apply to extract the target constituent from natural products.^[55-61] Fundamentally, MAE method is different from conventional extraction methods because this extraction occurs as a result of changes in cell structure caused by electromagnetic.^[58]

Kaufmann and Christen^[62] have explained the mechanism of extraction process of the MAE method in more detail and has been clarified by Mandal *et al.*,^[56] Routray and Orsat,^[58] Périno-Issartier *et al.*,^[63] Zhang, *et al.*,^[64] and Sagarika, *et al.*^[65] As can be seen in Figure 1 that has been described by Périno-Issartier *et al.*, in the MAE method involves three steps: (1) separation of solutes from the active side of the sample matrix due to increased temperature and pressure; (2) solvent diffusion across the matrix sample; and (3) the solute release of the matrix sample by the solvent.^[63] Based on these mechanisms, some advantages of MAE methods such as rapid extraction, reducing gradient thermal, and increase the extract yields. In addition, the MAE method is also recognized as a green technology because it reduces the use of solvents.^[56,58,63,64] The MAE method was first introduced and patented as an extraction method for organic compounds by Pare in 1995.^[66] However, it has begun to be applied to extract essential oils from *Cordia curassavica* by Gómez and Witte in 2001.^[67]

The principle of heating using microwave energy is based on the direct effects of microwaves on material molecules.^[62] The transformation of electromagnetic energy occurs through two mechanisms, namely, ionic conduction and dipole rotation in both solvents and samples. In many applications, these two mechanisms co-occur, which effectively convert microwave energy to thermal energy.^[56,58,62-64]

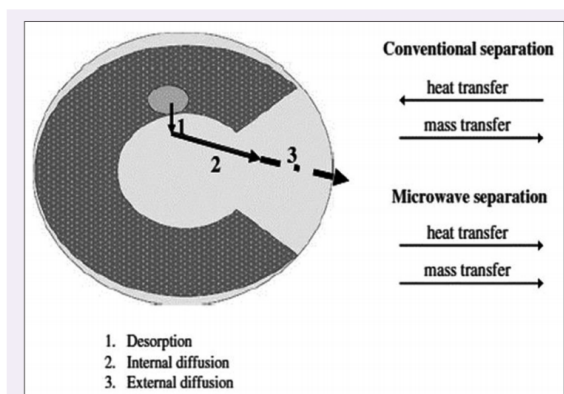


Figure 1: The fundamental difference between heat transfer mechanism and mass in microwave-assisted extraction method and conventional methods (source obtained from Perino-Issartier S., *et al.*, 2010)

Application of MAE method to extract secondary metabolites of the natural product has been successfully reported. Some studies have been reported including essential oil extraction from *C. curassavica*,^[67] polyphenols and caffeine extraction from green tea leaves,^[55] flavonoid extraction of *Radix Astragali* (*Astragalus mongolicus*),^[68] phenolics compound extraction from peanut skins and wine lees,^[57,69] phenolic compound extraction from *Gordonia axillaris*,^[70] bioactive alkaloid extraction of *Stephania sinica* and *N. nucifera*,^[59,71] polyphenolics compound extraction from selected medicinal herbs grown in Turkey (including *Hypericum scabrum* L., *Papaver fugax* Poiret var. *platydiscus* Cullen, and *Achillea vermicularis* Trin.),^[61] optimization of green tea waste extraction,^[72] extraction of active compound from *P. pellucida* (L.) Kunth,^[73] and others.

Application of ionic liquid-based microwave-assisted extraction to extract secondary metabolites from herbal plant

The use of the IL-MAE method in the development of extraction method to obtain the optimum targeted compound of natural products. As has been described by Bogdanov at chapter 7 in the book entitled "Green Chemistry and Sustainable Technology: Alternative Solvent for Natural Products Extraction,"^[18] some essential factors must be considered to obtain optimal results in the extraction process from natural materials as shown in Figure 2. One of the critical factors to think and focus on this review article is the selection of extraction methods (especially the MAE methods). The utilization of MAE method combined with ILs as a green solvent has been successful and has been done since 2007,^[9] although the use of ILs as a solution has been applied since 2003.^[74]

The IL-MAE method has advantages over other conventional means, besides provides higher yields and shorter extraction time but has also examined economics and environmental impact standpoint as a green solvent. For example, research has been conducted by Du *et al.* shows that resveratrol extraction using ILs is better than using conventional methods as well as MAE methods with conventional organic solvents (methanol),^[9] as well as in other plant species such as *Psidium guajava* and *Smilax china*.^[38] As for the other target group, compounds also successfully performed such as alkaloids,^[10] polyphenols,^[11] flavonoid,^[16] essential oils,^[11] and other. The optimum condition of IL-MAE depends on the sample matrix of plant and the type of ILs selected, but some terms that are parameters in the optimization process of the IL-MAE [Table 2] include microwave power, ILs concentration,

Table 2: Application of ionic liquid-based microwave-assisted extraction to extraction the targeted compound from the herbal plant

Herbal plant	Targeted compound	IL used	IL-MAE method and optimum condition	References
<i>Polygonum cuspidatum</i> Sieb.et.Zucc	<i>Trans-resveratrol</i>	[BMIM] Br	2.5 M [BMIM] Br, temperature of 60°C, extraction time of 10 min, particle size of 0.3-0.4 mm, liquid-solid ratio of 20 ml/g	[9]
<i>Illicium verum</i>	Essential oils	[BMIM][PF ₆]	[BMIM][PF ₆], microwave power of 440 W, temperature of 100°C, particle size<0.4 mm, liquid-solid ratio of 20:1.5 (ml/g)	[11]
<i>Cuminum cyminum</i>	Essential oils	[BMIM][PF ₆]	[BMIM][PF ₆], microwave power of 440 W, temperature of 100°C, extraction time of 20 min, particle size<0.4 mm, liquid-solid ratio of 20:1.5 (ml/g)	[11]
<i>Cinnamomum</i> spp.	Essential oils Proanthocyanidins	[BMIM] Br	0.5 M [BMIM] Br, microwave power of 230 W, extraction time of 15 min, and liquid-solid ratio of 10 ml/g	[13]
<i>Rosa sinensis</i>	Quercetin	[OMIM] Br	2.5 M [OMIM] Br, temperature of 70°C, extraction time of 20 min, and liquid-solid ratio of 40 ml/g	[14]
<i>Scutellaria baicalensis</i> Georgi	Kaempferol Flavonoids	[OMIM] Br	1.0 M [OMIM] Br, microwave power of 400 W, extraction time of 90 min, liquid-solid ratio of 6 ml/g	[16]
<i>Peperomia pellucida</i> (L) Kunth	Total polyphenolic content	[BMIM] BF ₄ , [BMIM] Cl, [BMIM] Br, [EMIM] Br	0.79 mol/L [BMIM] BF ₄ , extraction time of 18.5 min, liquid-solid ratio of 10.72 ml/g, and microwave power 270 W	[18]
<i>Radix puerariae</i>	Isoflavone	[BMIM] Br	0.8 mol/L [BMIM] Br, microwave power of 600 W, extraction time of 5 min, temperature of 80°C, and liquid-solid ratio of 20 ml/g	[41]
<i>Nelumbo nucifera</i> Gaertn	Phenolic alkaloid [liensinine, isoliensinine, and neferine)	[BMIM][BF ₄], [HMIM][BF ₄]	1.5 M [BMIM][BF ₄] and 1 M [HMIM](BF ₄), microwave power of 280 W, extraction time of 1.5 min, liquid-solid ratio of 15 and 10 (ml/g), respectively	[10]
<i>Nelumbo nucifera</i>	N-nornuciferine, O-nornuciferine, Nuciferine	[HMIM] Br	1 M [HMIM] Br, microwave power of 280 W, extraction time of 2 min, liquid-solid ratio of 30 ml/g	[76]
<i>Dysosma versipellis</i>	Podophyllotoxin	[BMIM][BF ₄]	0.6 g/ml [BMIM][BF ₄], temperature of 50°C, extraction time of 10 min, liquid-solid ratio of 10 ml/mg	[81]
<i>Sinopodophyllum hexandrum</i>	Podophyllotoxin	[DEMIM][BF ₄]	0.8 g/ml [DEMIM][BF ₄], temperature of 60°C, extraction time of 10 min, liquid-solid ratio of 10 (ml/g)	[81]
<i>Diphylleia sinensis</i>	Podophyllotoxin	[AMIM][BF ₄]	0.4 mg/mL [AMIM][BF ₄], temperature of 50°C, extraction time of 15 min, liquid-solid ratio of 10 (ml/mg)	[81]
<i>Rosmarinus officinalis</i>	Carnosic acid Rosmarinic acid	[OMIM] Br	1 M [OMIM] Br, microwave power of 700 W, extraction time of 15 min, liquid-solid ratio of 12 (ml/g)	[82]
<i>Schisandra chinensis</i>	Essential oils Lignan	[C ₁₂ MIM] Br	0.25 M [C ₁₂ MIM] Br, presoaking for 4 hours, microwave power of 385 W, extraction time of 40 min, and liquid-solid ratio of 12 ml/g	[12]
<i>Myrica rubra</i>	Myricetin Quercetin	[BMIM][HSO ₄]	2.0 M [BMIM][HSO ₄], temperature of 70°C, extraction time of 10 min, and liquid-solid ratio of 30 ml/g	[83]
<i>Bauhinia championii</i> (Benth)	Myrcetin Quercetin Kaempferol	[BMIM] Br	2.0 M [BMIM] Br with 0.8 mol/l HCl, temperature of 70°C, extraction time of 10 min, particle size of<0.30 mm, and liquid-solid ration of 30 ml/g	[84]
<i>Dryopteris fragrans</i>	Phloroglucinols	[OMIM] Br	0.75 [OMIM] Br, temperature of 50°C, microwave power of 600 W, extraction time of 7 min, and liquid-solid ratio of 12 ml/g	[85]
Lemon Peels	Pectin	[BMIM] Br	0.1 M [BMIM] Br, temperature of 60°C, extraction time of 8 min, and liquid-solid ratio 20 ml/g	[86]
<i>Cajanus cajan</i>	Glycoside Flavonoid	[BMIM] Br	1.0 M [BMIM] Br, temperature of 60°C, extraction time of 13 min, and liquid-solid ratio of 20 ml/g	[87]
<i>Pseudo-nitzschia calliantha</i> H. Andr	Phenolic compound	[BMIM] BF ₄	0.5 M [BMIM] BF ₄ , microwave power of 700 W, temperature of 40°C, extraction time of 15 min, and liquid-solid ratio 20 ml/g	[88]

Contd...

Table 2: Contd...

Herbal plant	Targeted compound	IL used	IL-MAE method and optimum condition	References
<i>Gnetum gnemon</i>	Transresveratrol	[BMIM] Br	2.5 mol/l [BMIM] Br, microwave power of 90 W, extraction time of 10 min, liquid–solid ratio of 15 ml/g	[89]
Rice bran (<i>Oryza sativa</i>)	Gamma-oryzanol	[BMIM] PF ₆	1 M [BMIM] PF ₆ , microwave power of 270 W, extraction time of 10 min, liquid–solid ratio of 10 ml/g	[90]

IL-MAE=Ionic liquid based microwave-assisted extraction, IL=Ionic liquid, [OMIM] Br=1-octyl-3-methyl imidazolium bromide, [BMIM] Br=1-butyl-3-methyl imidazolium bromide, [BMIM] BF₄=1-butyl-3-methyl imidazolium tetrafluoroborate, [BMIM] Cl=1-butyl-3-methyl imidazolium chloride, [EMIM] Br=1-ethyl-3-methyl imidazolium bromide [HMIM] Br=1-hexyl-3-methyl imidazolium bromide, [BMIM][HSO₄]=1-butyl-3-methyl imidazolium hydrosulfate, [AMIM][BF₄]=1-allyl-3-methylimidazolium tetrafluoroborate, [HMIM][BF₄]=1-hexyl-3-methylimidazolium tetrafluoroborate, [BMIM] PF₆=1-butyl-3-methylimidazolium hexafluorophosphate, [BMIM][PF₆]=???, [C₁₂MIM] Br=DEMIM[BF₄]=???

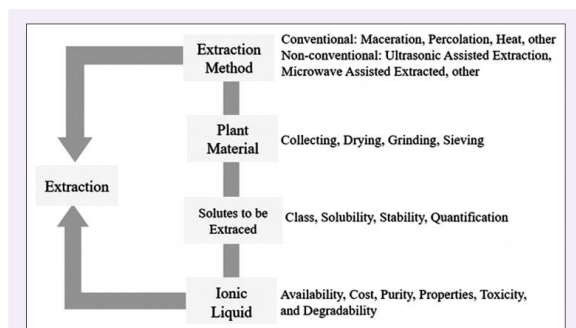
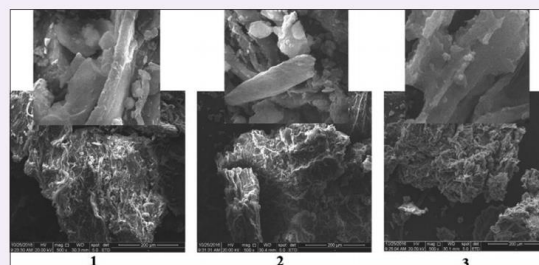


Figure 2: The main factors to be considered before extraction process

Figure 3: Scanning electron micrographs (×500 and ×10,000) of *Peperomia pellucida* aerial parts. Where (1) untreated samples, (2) extracted with maceration method using ethyl acetate, and (3) extracted with ionic liquid-based microwave-assisted extraction method using (BMIM)BF₄.

liquid–solid ratio, extraction time, temperature, pH, particle size of samples matrix, and so on.

Mechanism of ionic liquid-based microwave-assisted extraction method on extraction process

The mechanism of the IL-MAE method was first reported by Du *et al.* with measuring the kinetic of polyphenolic constituent extraction using an ILs as a green solvent.^[38] The mechanism of extraction was conducted using Fourier-transform infrared spectroscopy and scanning electron microscopy (SEM), by observing the extent of damage to the cell surface of the sample matrix. A study carried out by Du *et al.* showed similar mechanisms for quercetin and kaempferol extraction from *T. sinensis* and *R. sinensis* using IL-MAE with (BMIM) Br and (OMIM) Br.^[38] Ahmad *et al.* demonstrated that the surface and cell wall structures of *P. pellucida* sample was visibly destroyed after IL-MAE and maceration extraction treatment [Figure 3].^[91] A synergic reaction between microwave irradiation and the penetration of ILS solvent combination causes damage to the surface of the cell wall so that the secondary metabolite constituent contained in the sample matrix can pass through the damaged cell gap. The effect of extraction condition factors using the IL-MAE method in more detail on the extent of damage to the wall of the sample matrix was described in some literature.^[38,86,87,92,93]

Based on Figure 3, the SEM analysis results show significant physical changes in the plant tissue after treatment with different solvents. It was demonstrated differences in cell wall surface changes in samples that have been extracted using the IL-MAE method compared to maceration method and the untreated sample, whereas the ratio of the rate of surface changes of the cell wall the untreated sample and after the maceration extraction is not significantly different. The result of the SEM analysis

correlates with the yields value (total polyphenol content) generated by the maceration extraction and the IL-MAE extraction.^[91] Gross *et al.* (20) have explained the reason why cellulose can be dissolved in IL, but not in water, with the assumptions that anions of ILs can interact with hydroxyl protons from cellulose, and the coupling of cations to the side chain and oxygen binder strongly in peeling conditions.^[94] Payal *et al.* have also performed quantum chemical calculations on a group of solvent molecules to dissolve cellulose units, with the hypothesis that all intramolecular hydrogen bonds have been explicitly deleted on the ILs media because of the strong interaction of hydrogen bonds between cellulose and ILs.^[95] Thus, cell walls are easily damaged with ILs using heat extraction. That is the reason why extraction methods with heating or other nonconventional methods based on ILs take a short time compared to conventional organic solvent-based extraction methods. Therefore, the ILs solvent can be used as an alternative or green solvent which continues to be developed primarily for extracting the active components of medicinal plants with the aid of nonconventional extraction methods.

CONCLUSION

The application of IL-MAE method has been successfully performed to extract the targeted secondary metabolite from a natural product and provides higher yields and extraction rate with less solvent, short time (rapid), and energy consumption compared with conventional extraction method.

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9 Conflicts of interest

10 There are no conflicts of interest.

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