Ionic liquid-based ultrasound-assisted extraction: a novel insights of green extraction techniques for bioactive compounds from herbal plants

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ABSTRACT: The ionic liquid-based ultrasound-assisted extraction (ILUAE) is a non-conventional environmentally friendly extraction method. ILUAE is considered as green chemistry since ILUAE utilize ionic liquids as solvents and ultrasound-assisted extraction to extract bioactive chemicals from herbal plants. The growing popularity of ILUAE as preferred extraction method in herbal medicine is not only due to its sustainable, eco-friendly characteristics but also its improvement in extraction efficiency while maintaining the quality of extracted products. Here, we discussed and reviewed ILUAE as preferred extraction method for herbal medicines. Through discussing ILUAE’s potential, advantage against traditional extraction technique, and summarized the successful extraction of bioactive components from various herbal plants using ILUAE, we hope to showcase the technology’s efficiency, selectivity, and sustainability. Finally, we discussed current limitations and future challenge for ILUAE and potential ways to address these challenges.

KEYWORDS: Green extraction; herbal medicine; ionic liquid; ultrasound-assisted extraction.

INTRODUCTION

Herbal plants are becoming more popular due to their abilities as an essential source of herbal medicines compounds that can be used to develop new medications. By treating cancer and other illnesses, over twenty percent of all identified plants have been used in clinical studies, which benefits the healthcare system [1]. These medicinal products are also growing in popularity worldwide due to their all-natural origins, accessibility in local communities, affordability, simplicity of use, and perhaps no potential drawbacks. One of the most critical steps in the phytochemical processing process for identifying, separating, and recovering bioactive compounds from herbal plants is extraction. Sustainable extraction techniques must be used to reduce environmental damage while maintaining the quantity and quality of extracted products because the extraction and processing of natural products can, regrettably, negatively impact the environment [2], [3], [4]. Therefore, it becomes necessary to investigate novel, safer and more sustainable approaches for extracting bioactive compounds.

Over the past ten years, green chemistry has taken the lead in developing green engineering, redefining chemical procedures in both the academic and industrial domains [5], [6]. To improve the safety and environmental friendliness of the conventional separation methods for extracting the plant phytoconstituents with organic chemical reagents, Ionic Liquid (IL) are regarded as the most promising solvent for green chemistry because of their stability at high temperatures, non-volatility, non-toxic, stable molecularly, and adjustable mixability and polarity [7], [8]. The use of IL as a solvent is one example of how green chemistry...
principles are being increasingly applied to investigate the potential of active components from natural goods. Furthermore, when selecting solvents, economic and environmental implications must be considered [9].

The conventional method extraction techniques (such as soxhlet, maceration, and reflux) have several problems, including non-selectivity, poor extraction efficiency, high energy input, long workflows, and a tendency to use volatile, hazardous organic solvents, which could pollute the environment. Thus, the use of environmentally friendly and innovative extraction techniques, such as supercritical fluid extraction [10], microwave-assisted extraction [11], pressurized hot solvent extraction [12], and Ultrasound-Assisted Extraction (UAE) [13], is crucial these days to replace the conventional method while achieving high extraction yields along with preventing compound degradation. The best of those methods is UAE, which utilize acoustic cavitation to damage plant tissues, rupture cell membranes, and lessen mass transfer restrictions. The UAE method has also attracted a lot of attention due to significant decrease in time, temperature, the energy input and the amounts of organic solvent required for extraction, leading to improvement in kinetics of chemical reactions, higher solubility, as well as experimental repeatability in general [14].

One of the most enticing and promising new green extraction techniques arises from combining the benefits of IL and the advantages of UAE. The technique is then termed as the Ionic Liquid-based Ultrasound-assisted Extraction (ILUAE). Numerous studies have shown success using this extraction method. To name few, ILUAE have been demonstrated to extract *Chrysanthemum morifolium*’s isochlorogenic acid C at the optimum concentration [15], oleanolic acid from grape seeds [16], eight Ginsenosides from extraction of flower buds of *Panax Ginseng* [17], antioxidant compounds (namely curcumin, demethoxycurcumin and bisdemethoxycurcumin) from *Curcuma longa* L. [18], camptothecin and 10-hydroxycamptothecin from *Camptotheca acuminata* samara [19], aesculin and aesculetin from *Cortex fraxin* [20], four acetophenones from *Cynanchum bungei* Decne, a Chinese medicinal plant [21], polysaccharides and gingerols from *Zingiber officinale* Roscoe [22].

This article reviews an comprehensive review about the use of ILUAE as environmentally friendly extraction methods for the bioactive compound from herbal plants. Through this review, we would like to show the potential and advantage of ILUAE against traditional extraction technique. We aim to summarize the success of bioactive components extraction from various herbal plants using ILUAE along with the technology’s efficiency, selectivity, and sustainability. By conducting this review, we hope to provide some information that could be useful for future guidelines in the use of ionic liquid-based ultrasound-assisted extraction as green extraction technique from herbal plants. Finally, we discussed current limitations and future challenge for ILUAE and potential ways to address these challenges.

**METHODS**

This systematic literature review was conducted using PubMed, ScienceDirect, Google Scholar, Web of Science, and Scopus, without any time restrictions.

**DISCUSSION**

Ionic liquids as a green solvent in extraction process

The extraction and separation process are generally linked and should ideally be combined and carried out in a single phase. Current extraction separation methods have several drawbacks, including low efficiency and poor selectivity. In some cases where the final product’s cost increases, due to the complexity of the separation processes (such as chromatography), it needs a longer time and bigger more considerable energy. On top of that, severe circumstances and harmful volatile organic solvents are commonly used. Therefore, the concept of green solvents indicates a need to reduce the environmental impact of solvent consumption in chemical production [23]. Due to these disadvantages, researchers have been concentrating on developing
substitute extraction and purification methods that are "greener" and more sustainable, emphasizing the application of IL.

IL are organic salts or salt mixtures known as "green solvents" because of their excellent sustainable properties such as insignificant air pressure, melting temperature lower than its decomposition temperature (significantly below 100 °C or even at room temperature), non-flammability, extensive range of mixability with water and other organic solvents with outstanding chemical stabilities [24]. Moreover, IL is also reusable. Reusing IL preserves its properties and helps minimize solvent loss during extraction. According to Cláudio et al. (2013), 1-butyl-3-methylimidazolium chloride ([BMIM]Cl) can be recovered and utilized again after the caffeine extraction process from *Paullinia cupana* (guaraná). The IL solvent was recovered after the back-extraction procedure and used three more times without losing its ability to extract and its selectivity [25].

The use of IL as solvent in extraction process is that its high efficiency. When extracting biphenyl cyclooctene lignans from *Schisandra chinensis* Baill fruit, ILUAE outperformed conventional solvent-based extraction by a factor of 3.5 [26]. Whereas the conventional method required six hours for the extraction process, ILUAE completed it in just thirty minutes. Zeng et al. (2010) researched the use of methanol and various types of IL to extract rutin flavonoids. The 1-butyl-3-methylimidazolium bromide ([BMIM]Br) and 1-butyl-3-methylimidazolium tosylate ([BMIM][Tos]) showed the highest extraction yield, and the results is comparable with those of methanol extraction [27].

IL consist of a molecular structure that includes a variety of cations and anions. In contrast to the cations, which usually emerge as large organic complexes (carrying a positive charge), the anions are considerably smaller within volume and have an inorganic structure. To give illustration, let us compare salt and IL. The crystalline structure of salt is similar to IL (high resemblance between anion and cation in terms of size, load, and nature), but salt melts at high temperature (800 °C) and has a strong connection between its cation and anion [28]. The impact of anion and cation on IL was reported by Yang et al. (2011) which used ILUAE to extract two benzopyranoids from *Fraxinus rhynchophylla*, namely aesculetin and aesculin. The effect of the C4MIM anion, demonstrated an increase in extraction efficiency following their investigation of substitution of butyl for ethyl in the alkyl chain length. These can be explained as follows: butyl is more efficiently soluble in the two target analytes than ethyl. In contrast, the analysis of the cation revealed that, although the synthesis of [C4mim]Br only requires one step, synthesis of [C4mim]BF4 and [C4mim]ClO4 requires more time and money. Thus, [C4mim]Br was selected as the best solvent with extraction a range of 60–100% [29]. The authors also demonstrated that ILUAE offers high extraction yields by conducting a comparison study with conventional UAE using several molecular solvents, ethanol-based heating reflux, and simple stirring extraction.

The high polarity of IL is another remarkable feature. To ascertain the solvent polarity, a solvatochromic probe, such as Reichardt’s dye, typically shifts its charge-transfer absorption band when the solvent is present. The solvent and the phenoxide oxygen atom in Reichardt’s dye form a hydrogen bond, which causes the shift. The cation’s of imidazolium ring’s alkyl substituents' chain length and anion size decrease with increasing polarity. Temperature and the presence of water may impact the polarity values of IL. Ion-ion interactions, van der Waal forces, dipole interactions, and pi-pi interactions are another known factor that affect IL capability as solvent. Finally, it is important to evaluate how soluble IL are in water. It is known that the type of coordination possible with the ions will determine how much an element is soluble in water. Unlike the non-coordinating acidic and slightly coordinating neutral ions (BF4 and NTf2), basic ions (NO3), which often found in IL, could highly coordinate with water. Notably, the mixability of water in an IL also depends on the length of the alkyl chains on the cation. IL is known to become increasingly hydrophobic as its chains get larger [30]. Because of their strong polarity and capacity to dissolve a wide variety of molecules, including polar and nonpolar organic, inorganic, and polymeric compounds, IL are useful for chemical and biochemical reactions [31].

The ability to alter the molecules of IL—anion, cation, alkyl chain, and different substituents is another point of IL advantages. Thus, IL have been referred as "designer solvents" because their characteristics can be
changed to meet the needs of a particular procedure. Modifying the ion structure to change characteristics like density, hydrophobicity, viscosity, and melting point is simple. For example, Xiao et al. (2011) used [CnCim][BF₄] IL and showed that the extraction yield of β,β′-dimethylacrylshikonin from *Arnebia euchroma* (Royle) Johnst., which is hydrophobic, increases significantly with the alkyl chain length of the IL cation [32]. Another example is that the melting conditions of 1-alkyl-3-methylimidazolium tetrafluoroborates and hexafluorophosphates, which form liquid crystal forms of alkyl chain lengths longer than 12 atoms of carbon, are dependent on the size of the 1-alkyl group. In this case, 1-alkyl-3-methylimidazolium tetrafluoroborate salts are miscible with water at 25 °C when the alkyl chain length is less than six; nevertheless, they separate into an alternative phase when the alkyl chain length is more than six. This behavior enables the related solubilities of the ionic and extraction phases to be manipulated to make the separation as simple as possible, which can be highly beneficial when performing solvent extractions or product separations [33].

However, choosing IL for specific purposes could present a significant challenge because of the wide range of potential molecular interactions among IL. As such, selecting the optimal IL can be made more accessible by using a systematic approach and predictive thermodynamic models. This strategy also makes experimenting easier and less expensive[34]. Taken together, IL might be a preferable substitute for organic solvent (such as methanol) due to its advantages and few disadvantage.

Due to limitation of words, we summarized previous studies of IL (evaluated bioactive compounds and methodologies; IL names and acronyms, with their abbreviation, melting point, and density) in Table 1.

Table 1. Common IL were used as solvents for extraction from medicinal plants.

<table>
<thead>
<tr>
<th>Ionic Liquids</th>
<th>Abbreviation</th>
<th>Melting point °C</th>
<th>Density (g/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Allyl-3-methylimidazolim tetrafluoroborate</td>
<td>[AMIM][BF₄]</td>
<td>-88</td>
<td>1.231</td>
</tr>
<tr>
<td>1-Butyl-3-ethylimidazolium tetrafluoroborate</td>
<td>[BEIM][BF₄]</td>
<td>-82</td>
<td>1.200</td>
</tr>
<tr>
<td>1-Butyl-3-ethylimidazolium hexafluorophosphate</td>
<td>[BEIM][PF₆]</td>
<td>-8</td>
<td>1.380</td>
</tr>
<tr>
<td>1-Butyl-3-methylimidazolium chloride</td>
<td>[BMIM][Cl]</td>
<td>65</td>
<td>1.086</td>
</tr>
<tr>
<td>1-Butyl-3-methylimidazolium bromide</td>
<td>[BMIM][Br]</td>
<td>60</td>
<td>1.134</td>
</tr>
<tr>
<td>1-Butyl-3-methylimidazolium tetrafluoroborate</td>
<td>[BMIM][BF₄]</td>
<td>-71</td>
<td>1.208</td>
</tr>
<tr>
<td>1-Butyl-3-methylimidazolium bromide</td>
<td>[BMIM][Br]</td>
<td>60</td>
<td>1.134</td>
</tr>
<tr>
<td>1-Butyl-3-methylimidazolium hexafluorophosphate</td>
<td>[BMIM][PF₆]</td>
<td>10</td>
<td>1.373</td>
</tr>
<tr>
<td>1-Butyl-3-methylimidazolium trifluoromethylsulfonate</td>
<td>[BMIM][CF₃SO₃]</td>
<td>16</td>
<td>1.290</td>
</tr>
<tr>
<td>1-Butyl-3-methylimidazolium bis (trifluoromethylsulfonyl) amide</td>
<td>[BMIM][NtfO₂]</td>
<td>-8</td>
<td>1.404</td>
</tr>
<tr>
<td>1-Decyl-3-methylimidazolium bromide</td>
<td>[DeMIM][Br]</td>
<td>30</td>
<td>1.13</td>
</tr>
<tr>
<td>1-Ethyl-3-ethylimidazolium tetrafluoroborate</td>
<td>[EMIM][BF₄]</td>
<td>15</td>
<td>1.248</td>
</tr>
<tr>
<td>Ionic Liquid</td>
<td>Chemical Structure</td>
<td>Density (g/cm³)</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
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<td></td>
</tr>
<tr>
<td>1-Ethyl-3-ethylimidazolium hexafluorophosphate</td>
<td>[EMIM][PF₆]</td>
<td>1.373</td>
<td></td>
</tr>
<tr>
<td>1-Hexyl-3-methylimidazolium tetrafluoroborate</td>
<td>[HMIM][BF₄]</td>
<td>-82 1.075</td>
<td></td>
</tr>
<tr>
<td>1-Hexyl-3-methylimidazolium hexafluorophosphate</td>
<td>[HMIM][PF₆]</td>
<td>-61 1.304</td>
<td></td>
</tr>
<tr>
<td>1-Octyl-3-methylimidazolium tetrafluoroborate</td>
<td>[OMIM][BF₄]</td>
<td>-65 1.11</td>
<td></td>
</tr>
<tr>
<td>1-Octyl-3-methylimidazolium methyl sulfate</td>
<td>[OMIM][MS]</td>
<td>14 1.32</td>
<td></td>
</tr>
<tr>
<td>1-Octyl-3-methylimidazolium chloride</td>
<td>[OMIM][Cl]</td>
<td>0 1.000</td>
<td></td>
</tr>
<tr>
<td>1-Propyl-3-methylimidazolium tetrafluoroborate</td>
<td>[PMIM][BF₄]</td>
<td>-75 1.294</td>
<td></td>
</tr>
<tr>
<td>N-methylpyrrolidinium bis (trifluoromethylsulfonyl) amide</td>
<td>[MPPyr][Ntf₂]</td>
<td>0 1.44</td>
<td></td>
</tr>
<tr>
<td>Ethylammonium formate (BAF)</td>
<td>[NH₄H][HCO₃]</td>
<td>-10 0.99</td>
<td></td>
</tr>
<tr>
<td>N-butylnpyrrolidinium bis (trifluoromethylsulfonyl) amide</td>
<td>[BMPyrro][Ntf₂]</td>
<td>-50 1.4</td>
<td></td>
</tr>
</tbody>
</table>

**Ultrasonic-assisted extraction**

Extraction techniques originally aimed to increase the yield and purify the molecular target while maintaining its properties [35]. Alkaloids [36], flavonoids [37], glycosides [38], phenolic compounds [39], and polysaccharides [40] are among the therapeutic chemicals that have been successfully extracted from plants in laboratory studies using UAE. UAE is becoming increasingly popular due to several advantages over traditional extraction techniques, including lower energy usage, shorter extraction times, less harm to active compounds, and higher extraction yields [41]. The variables associated with UAE, such as power, duty cycle, temperature, time, solvent type, and liquid-solid ratio, must be controlled for effective extraction [42]. Ultrasound is also commonly used in solid/fluid media, regardless of whether the fluid is a liquid or a gas. Because of the difficulties in transmitting ultrasound due to imbalances in impedance and air absorption, solid/gas systems have rarely been used [43].
Figure 1. Ultrasound-assisted extraction mechanism: (A) plant cells were affected by ultrasound by producing cavitation bubbles; (B) the ultrasonic effect caused plant cells to rupture; and (C) the ruptured cell released bioactive compound.

As shown in Figure 1, the UAE mechanism depends on the transmission of ultrasound waves leading to cavitation within the solution; the cavitation bubbles collapse due to an increase in pressure caused by the ultrasonication process, which occurs at a frequency of 20 to 40 kHz. This ultimately results in deterioration of cellular wall and release of bioactive substances into the solvent. Acoustic cavitation during sonication creates cavitation bubbles that break down the plant cell wall and eventually make it easier for the solvent to seep into the extractable substance. To be more specific, sonication, or ultrasonication, is used to rupture cell membranes, which significantly reduces extraction time and optimizes extracted yield. When cavitation bubbles become sufficiently massive, the rarefaction cycle might exceed the binding forces between the liquid molecules. Brittle materials shatter due to localized heating brought on by the liquid jet's high velocity. The targeted compounds break out of the plant cell when they rupture due to the solvent medium entering along the pressure that the cell wall produces. [44], [45], [46], [47].

Ultrasonic technology is the preferred method for extracting plant bioactive compounds due to its high extraction yield. According to Mahindrakar and Rathod (2020), bioactive substances with 1.2 times increased antioxidant capacity could be extracted from jamun seed powder under optimum conditions. These included a 12-minute extraction time, a 1:15 solid-to-water ratio, an extraction temperature of 35 °C, a power of 125 W, and an operation cycle of 60%. Another study on baobab seeds' high phenolic compound discovered that the UAE process performed in about 20 minutes, 30% amplitude, 60°C temperature, and 30 ml/g solvent to solid ratio led to extract with higher flavonoid levels and antioxidant activity when compared to conventional extraction methods [49].

To reduce extraction time, the UAE has been combined with other approaches. Due to its shorter extraction time and lower hydro trope concentration, ultrasound-assisted hydro tropic extraction was a considerably more effective and sustainable option than hydro tropic extraction. [50]. However, the UAE is affected by the type of solvent used. To overcome this obstacle, usage of IL rather than traditional organic solvents with ultrasound extraction assistance is a preferred solution. For example, the amount extracted of carotenoids from orange peels, for instance, increased fourfold when 1-n-butyl-3-methylimidazolium tetrafluoroborate, an ionic liquid, was used as opposed to acetone solvent (7.8 8 ±0.59 μg/g to 32.08 ±2.05 μg/g) [4].

Application of ionic liquid-based ultrasonic-assisted extraction

One of the most appealing and promising methods of extraction offered currently is the ILUAE. Developing an environmentally sustainable protocol will benefit greatly from combining IL usage and ultrasonic technology. Compared to the conventional extraction method using IL as the solvent, the ultrasound
and IL combination was frequently found to be more beneficial in terms of efficiency, yield, selectivity, reaction time, reusability, and/or the production of unexpected products in some instances [51]. For example, there are two ways to extract widely recognized clinical antitumor drug paclitaxel (compound 169), a diterpenoid found in various Taxus species. The first was to soak the plant in a 95% ethanol and water mixture for 16 hours at room temperature, while the second used methanol with a reflux extraction method. The process of both extraction ways takes a long time. Therefore, Tan and his coworkers used MIL [C₄mim]FeCl₃Br and a methanol solvent to extract paclitaxel from Taxus species by optimizing several parameters, such as the amount of IL, the solid-liquid ratio, and the ultrasonic time. As a result, the yield was increased to 0.224 mg/g. [52] Another example by Cao et al. (2009) used an ultrasound preparation (ultrasonic bath, 40 kHz) in imidazolium-based IL to extract piperine from white pepper. All that needed to be done was to apply low-frequency ultrasound to the powdered sample in a water/IL mixture. The sample was then filtered and diluted, and the resulting solution was analyzed with an ultra-performance liquid chromatography instrument. No IL-related impacts were seen in the peak resolution, elution cycle, or elution duration [53].

Here, we have summarized some of the studies using ILUAE to extract bioactive compounds from herbal plants in Table 2. The table summarizes the types of IL used in the studies and the optimal state of ILUAE, depending on the plant background and type of IL selected, along with the system used for high extraction efficiency.

Table 2. Some studies on the application of ultrasound-assisted extraction based on ionic liquids to extract target compound from medicinal plants.

<table>
<thead>
<tr>
<th>Source</th>
<th>Compounds</th>
<th>IL</th>
<th>Optimum condition</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hang Fang Ji (Stephania tetrandra)</td>
<td>Fangchinoline, Tetrandrine</td>
<td>[BMIM][BF₄]</td>
<td>IL concentration: 1.5 M; solid/liquid ratio: 1:15 (g/mL); ultrasound: 150 W, 40 minutes</td>
<td>(73)</td>
</tr>
<tr>
<td>Madagasca r periwinkle (Catharanthus roseus)</td>
<td>Catharanthine, Vindoline and Vinblastine</td>
<td>[AMIM][Br]</td>
<td>IL concentration: 0.5 M; soak time of 2 h; solid–liquid ratio of 110 (w/v); ultrasound: 250 W, 30 min</td>
<td>(74)</td>
</tr>
<tr>
<td>Amur cork (Phellodendron amurense Rupr)</td>
<td>Berberine, Jatrorrhizine and Palmatine</td>
<td>[Br]</td>
<td>IL concentration: 0.3 M, solid-liquid ratio: 1:14 (g/mL); ultrasound: 100 W, 75 min</td>
<td>(75)</td>
</tr>
<tr>
<td>Sweet orange peels (Citrus sinensis (L.) Osbeck)</td>
<td>Carotenoids</td>
<td>[BMIM][Cl]</td>
<td>IL, co-solvent: proportion of 1:2; solid-liquid ratio: 1:3; and six extraction repetitions (5 min each), ultrasound probe: of 200 W, 20 kHz</td>
<td>(76)</td>
</tr>
<tr>
<td>Flax (Linum usitatissimum L.)</td>
<td>Secoisolariciresinol Diglucoside</td>
<td>[C₄mim][N(CN)₂]</td>
<td>IL concentration: 55.49% (w/w); solid-liquid ratio: 1:24.50; and ultrasound: 40 min</td>
<td>(77)</td>
</tr>
<tr>
<td>Plant</td>
<td>Compound</td>
<td>IL Concentration</td>
<td>Solid-Liquid Ratio</td>
<td>Ultrasound</td>
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<tr>
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</tr>
<tr>
<td>Cocoa</td>
<td>Caffeine and Theobromine</td>
<td>4.5 M; 1:6</td>
<td>300 W (theobromine), 100 W (caffeine)</td>
<td></td>
</tr>
<tr>
<td>Moso bamboo</td>
<td>Flavonoids (Isoorientin, Orientin, Vitexin and Isovitexin)</td>
<td>1.5 mol/L; 1:41</td>
<td>300 W, 90 min</td>
<td></td>
</tr>
<tr>
<td>Black Pepper</td>
<td>Piperine</td>
<td>2.0 M; 1:15</td>
<td>500 W, 30 min</td>
<td></td>
</tr>
<tr>
<td>Ginseng</td>
<td>Eight ginsenosides (ginsenoside-Rg1, -Rg2, -Rf, -Rb1, -Rc, -Rb2, -Rb3 and -Rd)</td>
<td>0.3 M; 1:10</td>
<td>20 min</td>
<td></td>
</tr>
<tr>
<td>Juan bai</td>
<td>Amentoflavone and Hinokiflavone</td>
<td>0.15 mol/L; 1:12</td>
<td>280 W, 30 min</td>
<td></td>
</tr>
<tr>
<td>Asian Liquorice</td>
<td>Isoliquiritigenin</td>
<td>0.3 mol/L; 1:15</td>
<td>100 W, 120 min</td>
<td></td>
</tr>
<tr>
<td>Goji berry</td>
<td>Zeaxanthin</td>
<td>0.09 g/mL; 1:40</td>
<td>420 W, 39 min</td>
<td></td>
</tr>
<tr>
<td>Chinese ash</td>
<td>Aesculin and Aesculetin</td>
<td>0.86 M; 1:10.55</td>
<td>250 W, 44 min; 4 h soaking time</td>
<td></td>
</tr>
<tr>
<td>Kudzu Root</td>
<td>Puerarin</td>
<td>1.06 mol/L; 480 W and 27.43 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baishouwu</td>
<td>Acetophenones</td>
<td>0.6 M;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plant</td>
<td>Compound(s)</td>
<td>Extraction Conditions</td>
<td></td>
<td></td>
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<tr>
<td>----------------------------</td>
<td>-----------------------------------------------------------------</td>
<td>---------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(Cynanchum bungei</em> Decne)</td>
<td>Hydroxyacetophenone, 2,5-dihydroxyacetophenone, baishouwubenzophenone and 2,4-dihydroxyacetophenone</td>
<td>Ultrasound: 175 W, 50 min, 25 °C, particle size of 60–80 mesh</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(Magnolia-vine</em></td>
<td>Schizandrin, Schisantherin A, Deoxyxchizandrin, and ϒ-Schizandrin</td>
<td>IL concentration 0.8 M; solid-liquid ratio 1:12; 3 times and 4.0 h; ultrasound: 200 W, 30 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(Schisandra chinensis</em> Baill)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(Vine tea</em></td>
<td>Dihydromyricetin</td>
<td>IL concentration 1.25 mol/L; solid-liquid ratio 1.45 (g/mL); ultrasound: 240 W, 5.5 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(Ampelopsis grossedentata)</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(Japanese honeysuckle</em></td>
<td>Caffeoylquinic acids</td>
<td>IL concentration 1 mol/L; solid-liquid ratio 1:50 (g/mL); ultrasound: 10 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(Flos Lonicerae Japonicae)</em></td>
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<tr>
<td><em>(Grape seeds</em></td>
<td>Oleanolic acid</td>
<td>IL concentration 0.7 mol/L; solid-liquid ratio of 1:15 (g/mL); extraction time of 4 h; ultrasound: 195 W, 13 min, 48 °C</td>
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<tr>
<td><em>(Vitis vinifera</em> L.)</td>
<td></td>
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<tr>
<td><em>(Dahurian larch</em></td>
<td>(+)-catechin, (-)-epicatechin, procyanidin dimers B2 and B4, and procyanidin trimer C1</td>
<td>IL concentration 1.25 M; soak time 3 h; solid-liquid ratio 1:10; ultrasound: 150 W, 30 min</td>
<td></td>
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<tr>
<td><em>(Larix gmelini</em> bark)</td>
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<tr>
<td><em>(Chinese goldthread</em></td>
<td>Berberine</td>
<td>IL concentration 0.5 M; solid-liquid ratio of 1:30 (g/mL); ultrasound: 100 W, 30 min</td>
<td></td>
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<tr>
<td><em>(Coptis chinensis)</em></td>
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<tr>
<td><em>(Maidenhair tree</em></td>
<td>Bilobetin, Ginkgetin, Isoginkgetin and Sciadopitysin</td>
<td>IL concentration 0.148 mol/L; solid-liquid ratio 1:14 (g/mL); ultrasound: 280 W, 25 min</td>
<td></td>
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</tr>
<tr>
<td><em>(Ginkgo biloba</em> L.)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| **Ginseng**  
(Flowe Buds of *Panax Ginseng*) | Ginsenoside Rg1, Re, Rf, Rg2, Rb1, Rb2, and Rd | IL concentration  
0.23 M; solid-liquid ratio 1:31; ultrasound 23 min, 30 °C | (17) |
|---|---|---|---|
| **Florist’s daisy**  
(*Chrysanthemum morifolium*) | Isochlorogenic acid C | IL concentration  
0.65 mol/L; solid-liquid ratio 1:23.44; ultrasound time 48.99 min | (15) |
| **Celery**  
(*Apium graveolens*) | Luteolin and Apigenin | IL concentration  
1.0 mol at pH 1.0; solid-liquid ratio 1:10; ultrasound: 200 W, 90 min | (91) |
| **Happy tree**  
(*Camptotheca acuminata samara*) | Camptothecin and 10-hydroxycamptothecin | IL concentration  
0.75 M; solid-liquid ratio 1:12; ultrasound: 239.42 W, 34.58 min | (19) |
| **Common Fig**  
(*Ficus carica* L.) | Gallic acid, chlorogenic acid, rutin, psoralen, and bergapten | IL concentration  
1.0 M; solid-liquid ratio of 1:50; ultrasound: 30 min, 30 °C | (92) |
| **Rosemary**  
(*Rosmarinus officinalis*) | Phenolic carboxylic acids, carnosic acid and rosmarinic acid | IL concentration  
1.0 M; 2 h soaking time; solid-liquid ratio 1:20; ultrasound: 220 W, 30 min | (93) |
| **Roof Iris**  
(*Iris tectorum* Maxim) | Tectoridin, iristectorin B and iristectorin A | IL concentration  
0.5 M; solid-liquid ratio 1:30; ultrasound time 30 min | (94) |
| **Turmeric**  
(*Curcuma longa* L.) | Curcumin, demethoxycurcumin and bisdemethoxycurcumin | IL concentration  
4.2 mol/L; solid-liquid ratio 1:30 (g/mL); ultrasound: 250 W, 90 min | (18) |
| **Oak galls**  
(*Quercus sp.*) | Gallic acids, Tannic acids | IL concentration  
0.10 M; solid-liquid ratio 1:10; 8 h | (85) |
| **Golden-bell**  
(*Forsythia suspensa* (Thunb.) Vahl) | Forsythosides I and A | IL concentration  
0.6 M; solid-liquid ratio 1:15 (g/mL); ultrasound time 10 min | (95) |
**Mechanism on extraction process of Ionic liquid-based ultrasonic-assisted extraction**

In their development of phenolic acid extraction from oak galls using an IL [BMIM][Tf$_2$N] as a green solvent, Sukor *et al.* (2020) explained the mechanism of the ILUAE method (Figure 2). They compared the sonicated samples to the non-sonicated ones, and the results showed a significant increase in extraction efficiency. The extraction is significantly affected by the initial stages of wetting and infiltration. The ability of solvents to infiltrate and the surface characteristics of medicinal materials are related to the infiltration impact caused by extraction solvents on those compounds. The ionic liquid can be added to improve extraction efficiency by changing the surface tension within the medicinal materials and the solvent, making it easier to penetrate and helps the solvent to enter the plant cells. On the other hand, adding ultrasonication at this point allows the solvent to enter cells faster and enhances the infiltration effect [54]. This phenomenon, called cavitation phenomena, could be the reason for the increased efficacy of the Ultrasonic Probe Assisted Extraction method used in this study. As compression and expansion are the primary characteristics of the extraction process, it is thought that the cavitation phenomenon results from the transmission of mechanical waves resulting from the combination of high pressure with low pressure. The sonication process creates acoustic cavitation, which has chemical, physical, and mechanical effects that cause the cellular wall to rupture and increase the solvent's penetration into the studied samples. This eventually makes it easier to extract the phenolic acids from the oak galls [14].

<table>
<thead>
<tr>
<th>Plant</th>
<th>Active compounds</th>
<th>IL concentration</th>
<th>Solid-liquid ratio</th>
<th>Ultrasound conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginger (Zingiber officinale Roscoe)</td>
<td>6-, 8-, 10-gingerols and ginger polysaccharides</td>
<td>[C$_2$MIM]BF$_4$</td>
<td>1.5 M; 1:20 (mL/g)</td>
<td>200 W, 10 min, 25 °C</td>
</tr>
<tr>
<td>Red sage (Salvia Miltiorrhiza Bunge)</td>
<td>Cryptotanshino ne, tanshinone I and tanshinone II A</td>
<td>[OMIM][Cl]</td>
<td>0.5 mol/L; 1:40 (g/ml)</td>
<td>105 W, 80 min</td>
</tr>
<tr>
<td>Chinese conifer needles</td>
<td>Shikimic acid</td>
<td>[BenzMIM][Br]</td>
<td>0.5 mol/L; 1:8.3 (g/mL)</td>
<td>170 W, 39 min</td>
</tr>
<tr>
<td>Purple fleabane (Psoralea corylifolia seeds)</td>
<td>Psoralen and isopsoralen</td>
<td>[C$_6$MIM][Br]</td>
<td>0.5 mol/L; 1:10 (g/mL)</td>
<td>437 W, 28 min, 313 K, 60~80 mesh</td>
</tr>
<tr>
<td>Peach flower (Amygdalus persica L.)</td>
<td>Isoquercitrin, trifolin and afzelin</td>
<td>[HMIM][PF$_6$]</td>
<td>1.0 mol/L; 1:40 (g/mL), 50 mesh</td>
<td>400 W, 40 min, extraction temperature 50 °C</td>
</tr>
</tbody>
</table>
Another study was also done by Kou and his coworker (2018), who successfully extracted polysaccharides and gingerols in one step by using [C₄mim]BF₄ as IL combined with ultrasonic assistant extraction. They observed the cell structure of ginger (Zingiber officinale Roscoe) using Scanning Electronic Microscopy (SEM) by viewing its microscopic structural alterations of ginger rhizome tissues in contrast to the conventional extraction methods displayed in Figure 3, which explore the impact of ILUAE on the matrix.

The SEM micrographs demonstrated how the samples were treated with various extraction techniques, and those left untreated broke down at the cell wall. The untreated sample’s cell walls were smooth and undamaged, as shown by the red circle in Figure 3A.

Following soxhlet extraction, the sample’s cell wall surface was wrinkled and rough, but the cell shape remained irregular and intact. Surprisingly, following ultrasound exposure (Figure 3B), the cell walls took on a jagged edge, and fragments of cells were visible on the surface; this suggests that the cavitation from applying ultrasound had transformed the cell walls into a release of target compound. In contrast, in the case of ILUAE (Figure 3C) compared to EUAE, the cell walls showed more apparent damage, and a large amount of cellular debris was found on the surface of the cell wall. These results indicated that the possibility of ultrasound damage was elevated by the IL [22].
Above all, it proved that IL combined with ultrasonic hold great promise as novel substitutes for traditional methods in extraction process applications. Furthermore, it has been demonstrated that ILUAE can increase the effectiveness of extracting herbal medicines.

**Limitation and future challenges of ILUAE**

The focus of new developments in environmental research development is on developing technologies that minimize risk and maximize chemical process efficiency while reducing and preventing pollution at its source. In this case, using ILUAE to create bioactive compounds might be considered a helpful technology for environmental chemistry since it permits the use of renewable raw materials, thereby reducing the requirement for energy and additional substances [55], [56].

There is a possibility that more encouraging chances will come from the ILUAE, as seen by the growing number of recorded examples. We specifically note the following limitations and upcoming difficulties in this review: (1) Due to its low vapor pressure, IL were first considered a green solvent that was safe for both human health and the environment when employed as a solvent in ILUAE. However, certain IL compromise their green credentials because they are made from non-renewable energy sources and degrade badly in the environment [57]. Thus, the significant challenges to using traditional IL have been their availability and cost. It is crucial to develop guidelines appropriate for designing ecologically safe IL; there are potentially millions of different combinations of ions in an IL. Alterations to the structures of the cations and anions result in changes to their lipophilicity and mixability with water, which are associated with increased biodegradability and toxicity to environments [58]. By testing the toxicity of existing IL, the factors responsible for toxicity can be identified, and the synthesis of new IL can be designed without risk to the environment. The toxicity of IL depends on many factors, such as cationic structure, alkyl chain length, concentration, and the specific resistance of the organism [59], [60], [61].

The registration, evaluation, and authorization of chemical (REACH) regulation of the European Union and the Organization for Economic Cooperation and Development (OECD) suggest employing Quantitative Structure-activity relationships (QSARs) to assist in designing new green industrial chemicals (IL) and predicting their toxicological and ecotoxicological properties [62], [63]. This QSAR model could make it possible to predict the (eco)toxicity of IL. When there are gaps in the data, computational modeling can be used to predict the toxicological effects of IL without any experimental support [64]. (2) The primary challenge of the ILUAE is determining the optimal ratio of acoustic power supplied to the reaction medium. Sufficient energy must be applied at low frequencies to maximize physical effects. Since ultrasonic baths are not always powerful enough, the highly different and viscous systems produced in IL frequently need a direct irradiation through an ultrasonic probe directly absorbed in the solution. On the other hand, depending on the type and purity of the IL, an excessively high acoustic power may cause a partial degradation of the IL. It is insufficient for writers to believe these issues could be fixed with more optimization and downstream processing; numerous studies have documented the irradiated IL becoming more intense over time; which can be potential serious issue on upscaling extraction process. Moreover, because these procedures can use a lot of energy and organic solvents, recovering or recycling the IL at the final stage of the process is still challenging. (3) Industrial applications will mix IL in ILUAE with other products, making effective IL separation and recycling necessary for ecological and financial reasons [65]. Numerous researchers have noted that the primary issue with IL usage is their relatively high cost, which highlights the need for more research on the recycling of IL [66], [67], [68]. Since IL are currently more expensive than conventional molecular solvents and are required in large quantities for various applications, effective IL recycling is crucial to their continued use, particularly for large-scale applications. In contrast, because of their increased production levels (to meet growing demand), IL should become more economically competitive with organic solvents, lowering their cost in the near future [69], [70]. To address the issue of cost, specific inexpensive and straightforward synthesis methods are necessary for the recycling and repurposing of the IL. For example, by extracting the DMF component using vacuum, IL recovered from simple combinations of IL and N,N-dimethyl formamide (DMF) could be recycled up to four times without exhibiting any notable loss in purity [70]. (4) The phenomenon of acoustic cavitation and the reduction in compound yield are affected mainly by the existence of water or some organic impurities in irradiated iron oxides [71].
another example, hot spots in a water or hydrophobic IL medium exposed to 20 kHz US irradiation preferentially occur in water instead of the IL. The primary explanations involve the variations in vapor pressure and viscosity between IL and water. The viscosity of the irradiated material may affect the acoustic cavitation [72].

**CONCLUSION**

The application of ILUAE, a green extraction approach, has been successfully employed to extract the targeted secondary metabolite from medicinal plants by providing a safer extraction method, higher yields, and extraction rate with less solvent, less time, and less energy consumption when compared to conventional extraction methods.

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**Conflict of interest statement:** The authors declared no conflict of interest.

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