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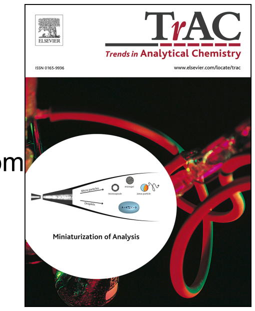

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IL-BASED ADVANCED TECHNIQUES FOR THE EXTRACTION OF VALUE-ADDED COMPOUNDS FROM NATURAL SOURCES AND FOOD BY-PRODUCTS

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ABSTRACT

In recent years, the use of ionic liquids (ILs) as green solvents for different extraction techniques has received great attention by their outstanding advantages over conventional organic solvents. ILs are considered environmentally-friendly solvents and they offer some advantageous properties to be used in extraction systems such as low toxicity; non-volatility; non-flammability; high ionic conductivity; and different polarity, hydrophobicity and selectivity. In this sense, their use in combination with advanced extraction techniques, such as microwave-assisted extraction (MAE), ultrasound-assisted extraction (UAE) or subcritical water extraction (SWE), is continuously increasing. This review presents an overview of the latest developments and applications of ILs combined with advanced extraction techniques to obtain bioactive compounds from natural sources and food by-products, which constitute a synergistic approach to contribute to the circular economy by revalorising waste and reducing the use of toxic solvents.

Keywords: ionic liquids, green extraction techniques, bioactive compounds, food by-products, natural sources.

Abbreviations: ILs, ionic liquids; MAE, microwave-assisted extraction; PLE, pressurized liquid extraction; RSM: response surface methodology; SFE, supercritical fluid extraction; SWE, subcritical water extraction; UAE, ultrasound-assisted extraction; UMAE, ultrasound/microwave-assisted extraction; VOCs, volatile organic compounds; ATPS, aqueous two-phase system.

1. Introduction.

Food by-products, such as stems, shanks, leaves, seeds, peels, shells, trimming residues, wastewater, and unusable pulp, are produced during food processing in large amounts around the world (about 38 % of the original weight of raw materials). The main current use of agro-industrial wastes is as fertilizers, biofuels or animal feed [1]. However, food by-products as well as their natural sources (medicinal plants, vegetables, fruits, roots, tubers, seeds, grains) represent an abundant source of value-added compounds which can be re-used for their potential healthy and rheological properties in different sectors such as cosmetics, food additives, pharmaceuticals, nutraceuticals, functional food, bioenergy, fertilizers, feed, textiles, packaging, biomaterials, etc. Growing interest has raised in recent years in food by-products valorisation as well as in the use of natural products with low toxicity instead of synthetic sources. This interest has led to much research in order to avoid environmental problems caused by the waste disposal in Nature, to increase the added value of the entire supply chain and to promote sustainability and circular economy approaches in food industries [2]. This interest has also led to the need of appropriate extraction methods to obtain bioactive compounds such as polysaccharides, sugars, minerals, dietary fibres, lipids, pigments, organic acids and phytochemicals (polyphenols, carotenoids), showing their high potential for health benefits related to their antibacterial, antioxidant, and anti-inflammatory properties, among others [3].

Bioactive compounds can be extracted by using conventional and non-conventional methods. Classical extraction techniques, such as Soxhlet extraction, maceration and hydrodistillation, are based on the extracting power of different solvents and the application of heat and/or mixing. The main drawbacks of these techniques are their low extraction selectivity, easy thermal decomposition of thermolabile compounds, use of costly high purity solvents, need of evaporating huge quantities of solvent and long extraction times. In contrast, non-conventional methods require lower amounts of synthetic and organic chemicals, reducing extraction time and giving better yields and selective extracts; in summary being more environmentally-friendly. Some of the most promising advanced non-conventional extraction techniques developed in the last years are microwave-assisted extraction (MAE), ultrasound-assisted extraction (UAE), subcritical water extraction (SWE), supercritical fluid extraction (SFE), pressurized liquid extraction (PLE), enzyme-assisted extraction (EAE), and pulsed electric field assisted extraction (PEF) [4]. Some of these techniques comply with principles set by the Environmental Protection Agency (EPA, USA) [5] and they can be considered as "green techniques" [6].

The design of sustainable and green extraction methods for natural sources and wastes has become a hot research topic in the last years in order to decrease the use of petrochemical solvents and generation of volatile organic compounds (VOCs). Most organic solvents are volatile, flammable, toxic and increase environmental pollution. These drawbacks have led industries to turn to greener solvents and move towards more environmentally-friendly processes. Among them, ionic liquids (ILs) play an important role as non VOC-forming solvents and they have been considered as the most adequate selection for extraction and separation of bioactive compounds from various origins [7]. ILs have been successfully applied as solvents, co-solvents and supporting materials for the separation of bioactive compounds and for the extraction and purification of target biomolecules in natural products due to their interesting properties, such as their non-flammability, high chemical and thermal stability, and solvent power [8] (**Figure 1**). Furthermore, the use of ILs allows the surpassing of the recalcitrance of natural samples by modifying their morphological structure and they can improve the efficient fractionation of lignocellulosic biomass into its main components, such as lignin, cellulose, hemicellulose, phenolics, due to their high selectivity. ILs have been reported to be used as pre-treatment or extracting sustainable solvents to obtain value-added biomolecules in the processing of different food waste such as peanut hulls, poultry feathers, crustacean shells and citrus and potato peels [9].

Figure 1.

In the last years, different reviews dealing with the use of ionic liquids as green solvents mainly in liquid/liquid extraction and liquid-phase microextraction have been published [10]. Their use as stationary or mobile phases in analytical separation techniques, such as gas chromatography, liquid chromatography and capillary electrophoresis, for the separation of complex samples, has been also reviewed [11,12]. The potential of ILs for CO_2 capture and fixation to value-added chemicals such as linear and cyclic carbonates and electroreduction of CO_2 to carbon-rich fuels in ILs has been recently reviewed [13]. The unique properties of ILs have been also explored for their use as solvents, microwave absorbers, reactants, additives or templates combined with microwave irradiation (as heating source) in the organic synthesis of different heterocyclic compounds and the preparation of inorganic nanomaterials, polymers, biomass-based composites and carbon-derived composites [14,15]. Furthermore, the application of ILs to replace conventional liquid or solid matrices in matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) or to develop optical sensors has been also reported [16]. However, there are no recent reviews dealing with the use of ILs as green solvents in combination with advanced extraction techniques to obtain value-added compounds from natural sources and food by-products. The purpose of this review is to provide an overview of the applicability of ILs as green solvents to extract these target compounds with advanced extraction techniques, such as MAE, UAE and SWE.

2. Ionic liquids as green extractive solvents in advanced techniques.

ILs are described as liquid organic salts that melt below 100 °C, constituted of an inorganic or organic anion and a large organic cation (**Figure 2**). Among the unique properties of ILs, one of their most interesting and advantageous is their great variety in composition and properties due to a large number of cation and anion combinations, conferring them the possibility of tuning their properties in terms of hydrophobicity and solution behaviour, viscosity, biodegradation ability, and toxicity [17]. In addition, ILs are non-volatile, non-flammable, non-explosive, minimally corrosive, highly polar, and miscible/non-miscible with organic solvents and/or water. They also show a low-charge density and low symmetry ions, a reasonable ionic conductivity, poor electrical conductivity, excellent thermal and chemical stability and liquid range (up to 300 ºC), negligible vapour pressure (supporting their green character) and favourable solvating properties for a range of polar and non-polar compounds, making them serviceable to be applied in every branch of chemistry, including organic chemistry, inorganic chemistry, biochemistry, physical chemistry and analytical chemistry [18,19]. These useful properties have increased the interest of ILs as "tailor-made solvents" to be used as attractive green alternatives to conventional volatile organic solvents (VOSs) in different applications to improve extraction processes [20], reducing the air route of environmental exposure to VOSs, since ILs do not vaporise into air [21].

Figure 2.

The first developments in ILs were described at the very beginning of the twentieth century evolving towards novel ILs based on their stability in water and air or new routes to obtain ILs produced from renewable resources, that are biodegradable and biocompatible or less toxic and environmentally sustainable [22], such as the synthesis of cholinium- and amino-acid based cations [23]. A wide range of ILs are currently available and they can be either synthesised by chemical synthesis, microwave-assisted synthesis, electrochemical synthesis and ultrasound-accelerated processes for specific purposes or commercial, but the most common cations are quaternary-ammonium and nitrogen-based, namely pyrrolidinium, pyridinium, piperidinium, or imidazolium; combined with anions such as chloride (Cl^-), bromide (Br^-), acetate ($[CH_3CO_2]^-$), hexafluorophosphate ($[PF_6]^-$) and tetrafluoroborate ($[BF_4]^-$). The modification of the anion structure has influence in properties like thermal stability and miscibility, while the length of the alkyl chain in the cation and/or its shape or symmetry may modify the viscosity, surface tension and density [24]. A new generation of ILs named deep eutectic solvents (DESs) based on more stable and hydrophobic anions such as $[(CF_3SO_2)_2N^-]$, amino or organic acids, sugars, alkylphosphates or alkylsulfates and cations such as choline have attracted considerable attention in recent years [15].

Figure 3 summarises the main physical and chemical properties of ILs that have being the object of some attention in analytical chemistry as extracting solvents. Many works dealing with the successful replacement of harmful solvents by ILs in different analytical methods for sample preparation have been reported. All of them have shown improved extraction efficiency, including liquid-phase microextraction, aqueous two-phase system extraction, solid-liquid extraction, liquid-liquid extraction and solid-phase microextraction. For example, Svinyarov et al. studied different hydrophilic ILs for the solid-liquid extraction of sesquiterpenic acids from roots of *V. officinalis* with IL-aqueous solvents, followed by their HPLC quantification. Different variables were considered to optimize the IL-assisted extraction, such as cation and anion type, IL concentration, extraction temperature and time, and solid/liquid ratio [25].

Figure 3.

Due to their ionic character, high solvation ability for organic, inorganic and organometallic compounds, improved selectivity and the synthesis of air- and water-stable ILs, the use of ILs in analytical chemistry for the extraction of value-added compounds from natural sources in combination with advanced techniques (mainly MAE, UAE and SWE) has significantly increased. Furthermore, ILs containing metal ions have been reported to provide additional functionalities such as optical, magnetic, or catalytic activities [15]. In addition, the permanent search of more profitable, efficient and "greener" solvents is another major reason behind this raising trend [26].

The favourable solvating properties of ILs for the extraction and separation of bioactive compounds are related to their ability to undergo many solvation interactions with both polar and non-polar molecules that can be tailored by the structural properties of the IL. Therefore, many ILs have shown as suitable extracting solvents for MAE, UAE and SWE. The high thermal stability of ILs, which is dependent on both the cation and anion, is also an important feature making them adequate for different extraction methods regardless of the temperature used in the process. In general terms, ILs should be stable enough to resist the heating temperatures of some extraction procedures. It has been reported that imidazolium-based cations show higher thermal stability than tetraalkylammonium cations, according to TGA and DSC analyses. The thermal stability of imidazolium-based ILs increases in the following order: $[Cl]^-$, $[Br]^-$, $[I]^-$ < $[BF_4]^-$ < $[CF_3SO_3]^-$ < $[NTf2]^-$ < $[PF_6]^-$. Moreover, IL-based organic anions have been reported to show higher thermal stability than those based on inorganic anions [18].

ILs viscosity is several dozens to hundred times higher than water at room temperature and it usually increases with IL concentration and decreases at high temperature and asymmetry of IL anions, being very important to be taken into account for the extraction of bioactive compounds with advanced techniques. The introduction of branched and/or longer alkyl groups increases the overall viscosity of ILs, which is regulated by changes in their intermolecular interactions, including hydrogen bonds and Van der Waals forces. ILs viscosity is also dependent on impurities and/or the presence of co-solvents. Moreover, ILs may be hydrophobic or hydrophilic and their solubility is dependent on the size of the anion, increasing the hydrophobic nature in the following order: $[Br]^-$ ~ $[Cl]^-$ < $[BF_4]^-$ < $[PF_6]^-$ < $[NTf2]^-$ < $[BETI]^-$. ILs solubility may be also modified by using different lengths of alkyl substituents in the cation, decreasing their polarity with long alkyl chains. For example, the combination of an imidazolium cation with BF_4^- or Cl^- results in a hydrophilic IL, whereas its combination with PF_6^- results in a hydrophobic IL [15].

Regarding melting point, it is strongly dependent on the level of asymmetry of the cation. Finally, the volatility of ILs, which is related to their advantageous low vapour pressure, has been reported to be higher for compounds having a symmetrical cation based on imidazolium than values for asymmetrical ions [27].

3. Ionic liquid-assisted extraction of value-added compounds from natural sources and food by-products.

The extraction of bioactive compounds from a variety of natural sources using ILs has shown great potential [28]. The role of ILs in the solid-liquid extraction processes is not only limited to the enhanced solute-solvent interactions, increasing the solubility of the target compounds, promoting also solvent-matrix interactions leading to sample matrix permeability modifications. 1-Alkyl-3-methylimidazolium, $[CnC1im]^+$, is one of the most investigated cations by the combination ability with a large number of anions. Cúrko et al. studied the potential of different imidazolium-based fluids: [C2mim][Br], [C4mim][Br], [C5mim][Br], [C7mim][Br], [C10mim][Br], [mim][HSO_4], [sC4mim][HSO_4] and [mim][CF_3CO_2] for the extraction of grape skin flavonoids (proanthocyanidins and anthocyanins) by comparing them to conventional organic solvents. Different behaviour was observed among ILs and structurally close compounds, anthocyanin-3-O-monoglucosides and their acylated derivatives, evidencing the possibility for application of specific ILs as selective solvents in extracting individual phenolic compounds [24].

Several ionic liquids have been reported to be able to fractionate lignocellulosic materials due to ILs selectivity in reacting with specific substrates [29]. ILs with different character have been studied as efficient pre-treatment solvents for biomass fractionation to produce high purity cellulose, hemicellulose and lignin fractions. 5-hydroxymethylfurfural (5-HMF), furfural and reducing sugars have been also obtained from lignocellulosic biomass using ILs with high efficiency [15]. Bernardo et al. reported the use of hydrogen-bond basic ([emim][OAc]) and hydrogen-bond acidic ([emim][HSO_4]) IL-type pre-treatments coupled with enzymatic saccharification on converting wheat straw and eucalyptus biomass residues to fermentable sugars [30]. The possibilities of acidic ILs to be directly applied for sustainable lignocellulosic biomass fractionation into main components within the biorefinery and bioeconomy concepts have been recently proposed as an integral way to valorise wheat straw into high added-value chemicals, by combining ILs with enzymatic hydrolysis to efficiently fractionate hemicelluloses, cellulose and lignin producing different streams of sugars and phenolic compounds [31].

Advanced extraction techniques such as MAE [32-35], UAE [36-38], accelerated solvent extraction (ASE) [39,40] and pressurised technologies (PLE) [41,42], such as supercritical fluid extraction (SFE) [43-45] and subcritical water extraction (SWE) [46,47], also called pressurised hot water extraction (PHWE), are commonly used to obtain value-added compounds. The extraction of bioactive compounds from natural sources and food by-products using ILs with water or organic solvents and combined with advanced extraction technologies has gained relevance in the last years following the new trends based on the twelve principles of green chemistry [48,49] (**Figure 4A**). Research in the use of ILs combined with advanced extraction techniques for extracting value-added compounds is mainly based on MAE and UAE by the possibilities offered to achieve high extraction yields within short time (**Figure 4B**); while only some published reports have been found dealing with the use of SWE combined with ILs.

Amongst the main high-value compounds extracted by these powerful combinations, alkaloids, terpenoids and flavonoids have been the top performers; followed by aromatic compounds, lipids, lignans and phenolic acids. Natural mixtures, such as saponins, suberin and essential oils have been also studied (**Figure 4C**). IL selection and concentration, pH, temperature and extraction time, solid/liquid ratio, ultrasonic/microwave power have been considered as the main experimental conditions to be controlled in these studies [22,50].

Figure 4.

3.1. IL-MAE.

Microwave-assisted extraction (MAE) is well-known as a rapid and attractive sample extraction technique providing a rapid heat transfer which combined with pressure can maximise yields of the targeted compounds extracted from biological matrices. MAE could be potentially combined with ILs based on their high thermal and chemical stabilities, which are important parameters that govern the suitability and long-term stability of the extraction process. Microwaves are transmitted as non-ionising electromagnetic energy, which can penetrate the matter and interact with polar molecules generating heat. Ionic conduction and dipole rotation are produced in polar molecules, which is dependent on the dielectric constant [51]. Ionic liquids with high polarity are heated rapidly and uniformly under microwave irradiation throughout the whole reaction volume, being considered as excellent microwave absorbers [15]. ILs should be stable enough to withstand the operating temperatures of the heating samples and should be able to efficiently absorb microwaves and dissipate energy swiftly through ionic conduction [52], resulting in a rapid heating rate of the solvent-sample mixture, cell walls and/or membranes disruption and fast extraction, which combined with the negligible vapour pressure of ILs may reduce air pollution. So, the synergistic use of ILs (as potential VOCs alternative solvents) and MAE could provide low time consumption and energy savings being considered in that way a green extraction approach to extract different compounds such as phenolics, essential oils, alkaloids, etc.

The use of ILs in MAE has been reported in the extraction of lipids from different algal species using 1-butyl-3-methylimidazolium hydrogen sulphate ([BMIM][HSO_4]) as well as for the extraction of polyphenols from turmeric with 0.3 mol/L 1-octyl-3-methylimidazolium bromide in only 8 min at 55 ºC, compared to 90 min required for UAE with other solvents [53].

Traditional methods, such as heat reflux extraction, were used for pectin and naringin extraction from pomelo peels and were compared with MAE and IL-based microwave-assisted extraction (IL-MAE). Enhanced extraction yields of 8.38 ± 0.20 mg/g and 291.60 ± 7.25 mg/g for naringin and pectin, respectively, were obtained by using IL-MAE compared with other extraction methods. Extraction time was also reduced from 180 min to 15 min and the operation power from 700 to 331 W for heat reflux extraction and both MAE-based methods, respectively [54]. A Brönsted acidic ionic liquid [$HO_3S(CH_2)_4$mim]HSO_4 was used for IL-MAE and the optimal conditions were studied by using response surface methodology (RSM) based on a Box-Behnken experimental design at three levels, being the extraction variables: microwave irradiation time, liquid/solid ratio, and microwave irradiation power.

The use of IL-MAE to obtain different value-added compounds from natural sources has been reported. Some examples are the extraction of resveratrol from Melinjo (*Gnetum gnemon L.*) seeds [55], curcuminoids from *Curcuma longa* L. [52], gallic acid, ellagic acid and essential oils from the leaves of *Eucalyptus camaldulensis* [56], alkaloids from lotus leaf and Nelumbo nucifera Gaertn, polyphenolic compounds from medicinal plants and essential oils from dried fruits of *Illicium verum Hook. f.* and *Cuminum cyminum L.* [57]. Fan et al. [58] also used IL-MAE to extract verbascoside from *Rehmannia* root, which is widely used as drug and functional food in East Asia. In this work, aqueous solutions of 10 imidazolium-based ILs with different anions and cations were selected to study their extraction ability: 1-decyl-3-methylimidazolium chloride, [C10mim]Cl; 1-octyl-3-methylimidazolium chloride, [C8mim]Cl; 1-benzyl-3-methylimidazolium chloride, [Bemim]Cl; 1-butyl-3-methylimidazolium bromide, [C4mim]Br; 1-butyl-3-methylimidazolium dicyanamide, [C4mim]$N(CN)_2$, 1-butyl-3-methylimidazolium trifluoromethansulfonate, [C4mim]CF_3SO_3; 1-hydroxyethyl-3-methylimidazolium chloride, [C_2OHmim]Cl; 1-butyl-3-methylimidazolium acetate, [C4mim]Ac; 1-butyl-3-methylimidazolium nitrate, [C4mim]NO_3; and 1-butyl-3-methylimidazolium chloride, [C4mim]Cl. The selection of the best IL to get more efficient extractions was based on their chemical structure, viscosity, hydrophobicity or their hydrogen bonding strength. Regarding the alkyl chain length, like in [C10mim]Cl, this study demonstrated the influence of ILs structure and the steric hindrance effect between the target compound and the IL. A similar behaviour was observed by other authors when using $[Bemim]^+$ as cation [59,60].

In another work, [Bmim] PF_6 was selected as the most adequate solvent for the extraction of gamma oryzanol from rice bran by IL-MAE. A Box-Behnken design with RSM was used for optimizing experimental conditions: 30 % microwave power, 10 min extraction time, 15 mL/g of liquid/solid ratio and 0.7 M $[Bmim]PF_6$ solution [61].

In summary, IL-MAE has been widely applied to extract several active compounds from natural sources, providing high yields and extraction rates and low solvent and energy consuming. Optimal extraction conditions usual in IL-MAE include microwave power ranging from 280-700 W, irradiation times from 1.5-40 min, solid/liquid ratio from 1:7-1:40 and temperatures from 50-105 ºC. Increasing solvent volumes could result in lower extraction efficiencies and initial sample soaking followed by several extraction cycles have been performed to increase extraction yields [62].

3.2 IL-UAE.

As it has been already described, MAE is an effective and rapid technique for extracting bioactive compounds from food by-products and natural compounds, but it is difficult to be up-scaled and somewhat energy consuming. UAE could be used as an alternative to MAE in particular for extracting thermolabile compounds at short times and room temperature, since UAE could enhance mass transfer mechanically with no need of heating. Ultrasonic waves promote solvent penetration and swelling of the natural material as a consequence of the formation and further collapse of gas bubbles into the bulk of the solvent, causing enlargement of the matrix pores and sometimes cell tissue disruption, facilitating an easier release of the target compounds [62]. Several works have reported the use of IL-based UAE for the extraction of different compounds from natural sources and biomass, such as glycosides, alkaloids, flavonoids and terpenoids. Different ILs varying cations and anions were studied as well as the influence of different conditions, such as ILs concentration, extraction time, ultrasonic power, temperature and solid/liquid ratio, on extraction yields [7]. Optimal extraction conditions used in IL-UAE include frequencies ranging from 20-60 kHz with ultrasonic powers and times in the range of 150-500 W and 20-90 min, respectively. In order to increase extraction yields, initial soaking of sample (2-8 h) and several extraction cycles

(3-5) can be performed, increasing the final time needed for extraction. Increasing temperature, ultrasonic frequency or power, and/or sonication time may result in the degradation of thermally unstable compounds [62]. However, the number of ILs studied in their combination with UAE is still very limited and more research is needed to correlate extraction yields with ILs properties [63].

Wang et al. [64] reported the extraction of flavonoids (FVs) from bamboo leaves by using IL-based ultrasound-assisted extraction (IL-UAE) with 1-butyl-3-methylimidazolium bromide ([Bmim] Br), which was selected from fifteen ILs with diverse structures, like carbon chains or anions. This IL was selected due to its availability to show strong π–π interactions with the parent nucleus of FVs, forming hydrogen bonds which are stronger than those obtained with water. The most influencing parameters in the process were optimized using RSM and the final extraction efficiency was expressed as the total flavonoids content (4.592 mg/g). This result was much higher than others obtained with traditional extraction methods.

An IL-UAE method was also reported for the extraction of four isoflavones (daidzin, genistein, genistin and daidzein) from soy products. Different 1-alkyl-3-methylimidazolium compounds were investigated and 1-hexyl-3-methyl-imidazolium bromide ([C_6MIM]Br) (1 M) was selected as the extracting solvent. Variables such as extraction time, IL concentration and solid/liquid ratio were also evaluated [65]. In another work, Thakker et al. extracted geraniol from Palmarosa leaves by studying four different water-soluble synthesized ILs, being *N*,*N*,*N*,*N′*,*N′*,*N′*-hexaethyl-propane-1,3-diammonium dibromide the most suitable solvent. Process parameters were optimized following a Taguchi method as well as the Box-Behnken response surface design. 1.73 % (w/w) yield of geraniol was obtained under optimised conditions (40 mL aqueous solution containing 10 % IL, 250 W ultrasound power and 18 min extraction time) [66]. IL-UAE was also applied as a promising technique to simultaneously extract gingerols and polysaccharides from ginger, evidencing the possibility to extract hydrophilic and hydrophobic bioactive compounds from plant materials in one step [67].

3.3. Other IL-combined techniques

Some studies have reported the combination of ILs with both MAE and UAE (IL-UMAE) for the extraction of natural bioactive compounds, as an integrated approach to combine the advantages of ultrasounds and microwaves. IL-UMAE was applied for the extraction of gallotannins from *Galla chinensis* using [C_4C1im]Br as the best solvent to obtain higher extraction efficiencies in 1 min compared with 6 h for IL-based UAE [63]. The use of ILs for the extraction of five anthraquinones (chrysophanol, rhein, emodin, aloe-emodin and physcion) from rhubarb was reported by following a rapid, simple, efficient and sustainable IL-UMAE approach. Optimal UMAE conditions were achieved by using 2.0 mol/L of 1-butyl-3-methylimidazolium bromide ([bmim]Br) solution, 2 min, 500 W microwave power and a solid/liquid ratio of 1:15 (g/mL). The obtained results were compared with those obtained under heat-reflux extraction (HRE), MAE and UAE, showing higher efficiencies (18.90-24.40 % enhanced) and shorter extraction times (from 6 h to 2 min) [57].

Quercetin, isorhamnetin, kaempferol, rutin and volatile essential oils were successfully extracted from seabuckthorn (*Hippophae rhamnoides* L.) leaves by using IL-based ultrasound/microwave-assisted simultaneous distillation extraction (IL-UMASDE) and RSM optimization. 1.0 M 1-butyl-3-methyl imidazole bromine salt ([C_4mim]), an extraction time of 34 min, microwave power of 540 W, liquid/solid ratio of 12 mL/g and a fixed ultrasonic power of 50 W were used, obtaining significantly higher yields compared with those obtained with UAE, IL-UAE, MAE and IL-MAE techniques [68].

In addition to IL-UMAE, IL-based ultrahigh pressure extraction (UPE) has been reported for the extraction of tanshinones from *Salvia miltiorrhiza* using 0.5 M of [C_8C1im][PF_6] in ethanol solution, obtaining high extraction yields with short processing times and low energy and solvent consumption [69].

All the above-discussed IL-based extraction methodologies show limitations for the extraction of bioactive compounds, which are thermosensitive, thermolabile, unstable and susceptible to oxidation in contact with air. To overcome these drawbacks, negative-pressure cavitation extraction (NPCE), which is developed under inert atmosphere at low temperatures, has been proposed. An IL-based NPCE method for the extraction of flavonoids from the roots of *Cajanus cajan* (pigeon pea) using [C8C1im]Br has been reported, suggesting that this technique could be useful for the extraction of natural compounds at the industrial scale [70].

3.4. IL-SWE

ILs have been used in combination with SWE for the separation and extraction of some natural-based resources. Subcritical conditions under increased temperatures and pressures result in high diffusivities, improving significantly the solvating power of water making it a suitable solvent for organics. In addition, the high thermal stability of some ILs (up to 400 °C) could be another appropriate property of ILs when combining them with SWE. IL-SWE has been reported for the extraction of phenolic compounds, such as gallic, chlorogenic, gentisic, protocatechuic, p-hydroxybenzoic, and caffeic acids, from brown seaweed obtaining 4 to 5-fold increases in extraction yields [71]. A decrease in ILs viscosity was obtained by using long alkyl chains through the combination with water, decreasing the van der Waal's interactions and favouring the extraction process.

The essential parameters to be controlled during extraction with ILs are their chemical structure and concentration, moisture level, enzyme concentration, pH, extraction temperature and time, and enzyme to substrate ratio. The combination of all these parameters results in more viscous and dense solvents than common organics, increasing in that way the possibilities of SWE for the specific extraction of polysaccharides from natural sources [72], such as the case of carrageenan extracted from red seaweed. The combination of ILs and SWE was also successful for the specific extraction of bio-based chemicals such as lipids from wet microalgae at high yields, with potential to be used as biofuels precursors after application of optimised conditions [73].

4. IL Challenges and limitations

Ionic liquids have attracted great interest as potential substituents for conventional organic solvents in the extraction of specific compounds from natural sources due to their non-volatile and greener behaviour. However, some concerns regarding toxicity and potential environmental impact of some ILs and their breakdown products are still pending, including thermal decomposition and hydrolysis during consumption and poor biodegradability in the environment. The green character of ILs has been also questioned since most of them are obtained from fossil sources. Furthermore, the presence of impurities in ILs due to their synthesis involving organic compounds requiring some purification steps could drastically alter their properties, such as viscosity, rate and selectivity of extractions, while affecting their potential toxicity and environmental impact [74]. The difficulty of ILs to be recovered and recycled at the industrial scale is also a critical issue that can consume great quantities of energy and have high cost, limiting their application in commercial extraction technologies [75] and preventing ILs to be really competitive with conventional solvents. The possibility of IL recovery and its reuse has been recently considered by using preparative chromatography enhancing the sustainability of the extraction process for lignocellulosic biomass valorisation by recycling the IL with a yield higher than 90 wt% [31]. Other different approaches have been successfully applied for the separation and purification of ILs and the corresponding target solutes such as back-extraction with organic solvents, hydrodistillation of volatile compounds, anti-solvent-induced precipitation, and partitioning in IL-based ATPS [62]. Nevertheless, it is expected that further research will be developed focusing on new effective, simple and cost feasible methods for ILs recovery in order not to discharge potential toxic compounds into the environment which may cause soil and groundwater contamination as well as further risks to human health and living organisms. However, it should be also considered that, since a wide range of ILs can be obtained by changing the cation and/or anion, it is possible to select more degradable and less toxic ILs for the required extraction application through rational design. These tailor-made physico-chemical and biological properties joined to the potential of ILs to increase the extraction yield of targeted compounds may offset those negative concerns and set the advantageous use of ILs, providing new stimulus and challenges to research in the field. In addition, the interest in bio-based ILs synthesised from renewable sources, such as amino acids, lignin and carbohydrates, is increasing as a clear possibility to obtain greener ILs [76]. However, large amounts of environmentally unfriendly and non-renewable reagents are usually consumed in the synthesis of some bio-based ILs and efforts have to be made to reduce the use of these chemicals in order to explore in depth more potential uses of bio-based ILs.

5. Conclusions.

In recent years, the use of ionic liquids (ILs) as green solvents has been substantially increased and new research in analytical chemistry has been reported due to the unique physico-chemical properties and tuning possibilities of ILs by altering their cationic or anionic moieties to extract bioactive compounds from natural sources and food by-products; such as polyphenols, essential oils, lipids, glycosides, alkaloids, etc. The possibilities of ILs in combination with advanced extraction techniques such as microwave-assisted extraction (IL-MAE), ultrasound-assisted extraction (IL-UAE), and subcritical water extraction (IL-SWE) can be considered as a real sustainable alternative to the use of conventional organic solvents; reducing solvent consumption and extraction times due to the stronger dissolving power of ILs and the multiple interactions provided by their ions. However, the application of ILs combined with green extraction techniques is not fully exploited yet, and new applications on the extraction of different value-added compounds from natural samples are expected to raise in the coming years. An efficient recycling of ILs after extraction is also an important economic and environmental issue to be considered and more approaches dealing with the separation and purification of both ILs and solutes are needed, which may also contribute the up-scaling of the developed extraction methods from lab-scale to an industrial scale in the future.

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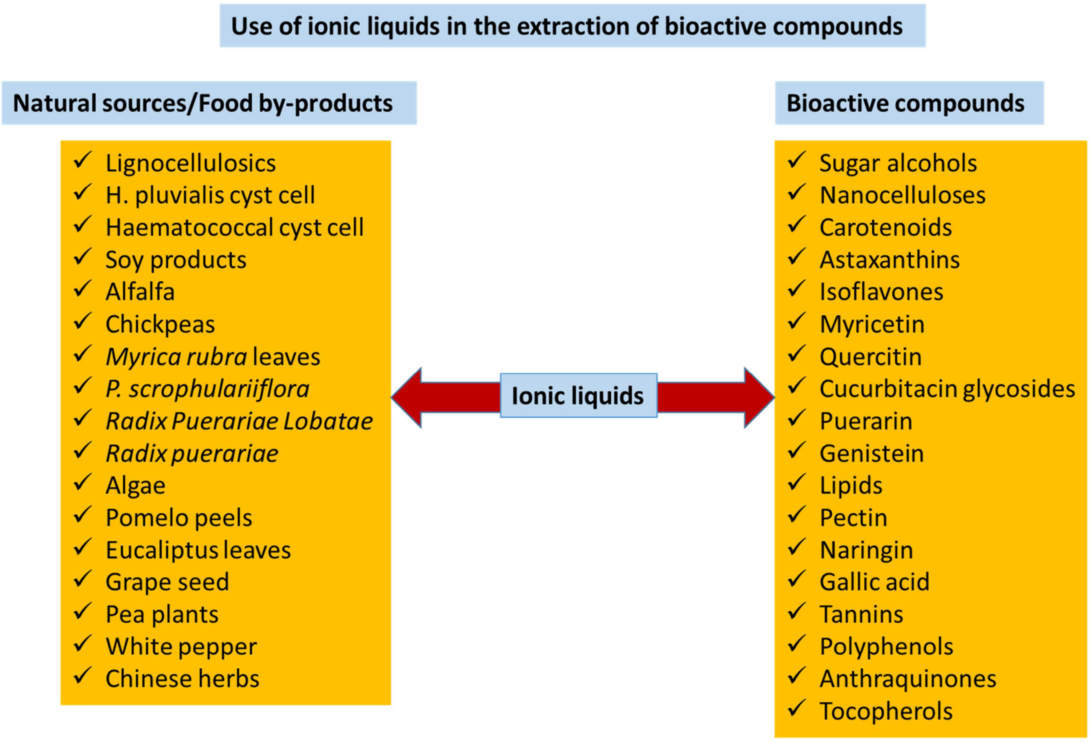

Figure 1. Extraction of bioactive compounds from natural sources and food by-products using ionic liquids.

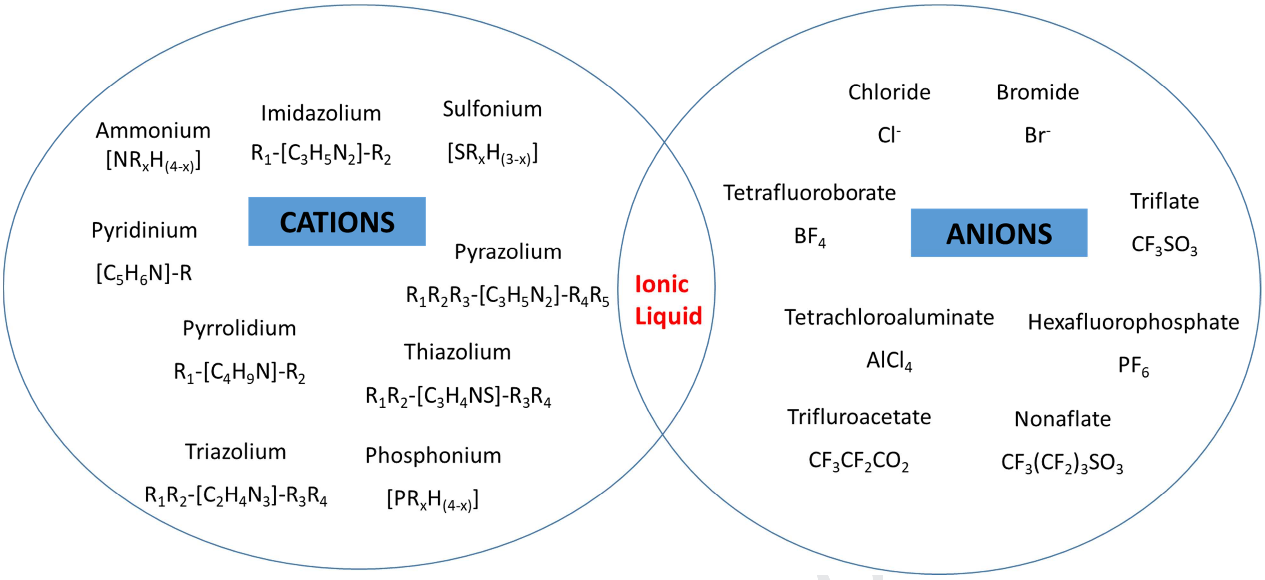

Figure 2. Most common cations and anions in ionic liquids.

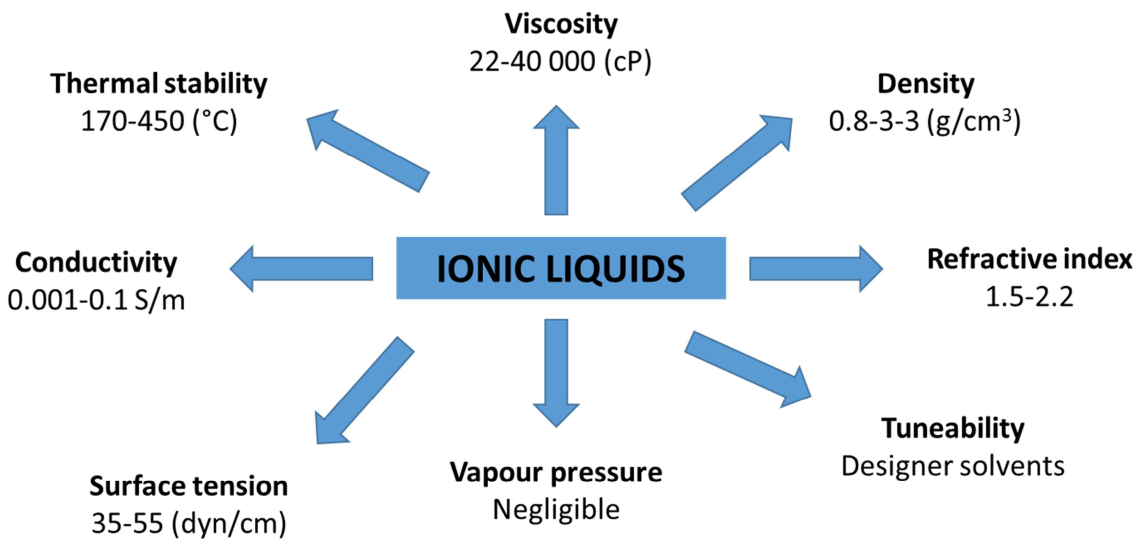

Figure 3. Main physico-chemical properties of ionic liquids as extracting solvents (adapted from Reference [74]).

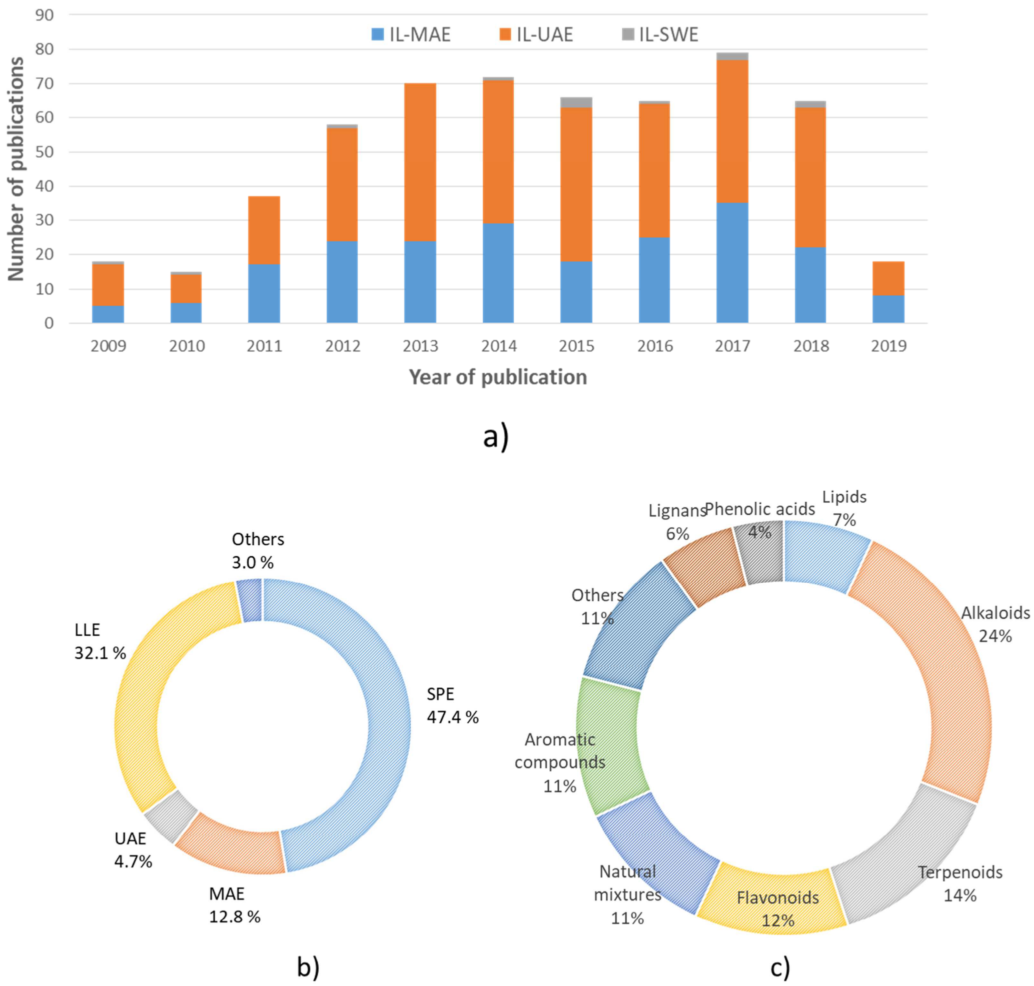

Figure 4. A: Number of publications combining ionic liquids with advanced extraction techniques (http://www.scopus.com). B: Distribution of works published based on IL-assisted extraction techniques for the extraction and separation of value-added compounds from natural sources in the last 5 years (http://www.scopus.com). C: Value-added compounds extracted from natural sources by family using IL- assisted extraction techniques (adapted from Reference [22]).

Highlights

Ionic liquids (ILs) as green solvents in advanced extraction techniques are reviewed

ILs for extracting bioactives from natural sources and food by-products are presented

Latest developments in ILs with green extraction techniques (MAE, UAE, SWE) are shown

ILs properties, challenges and limitations as extracting solvents are included