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ARTICLE TYPE

Ionic liquids solutions as extractive solvents of value-added compounds from biomass

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In the past few years, the number of studies regarding the application of ionic liquids (ILs) as alternative solvents to extract value-added compounds from biomass has been growing. Based on an extended compilation and analysis of the data hitherto reported, the main objective of this review is to provide an overview on the use of ILs and their mixtures with molecular solvents for the extraction of value-added compounds present in natural sources. The ILs (or ILs solutions) investigated as solvents for the extraction of natural compounds, such as alkaloids, flavonoids, terpenoids, lipids, among others, are outlined. The extraction techniques employed, namely solid-liquid extraction, and microwave-assisted and ultrasound-assisted extractions are emphasized and discussed in terms of extraction yields and purification factors. Furthermore, the evaluation of the IL chemical structure and the optimization of the process conditions (IL concentration, temperature, biomass-solvent ratio, etc.) are critically addressed. Major conclusions on the role of the ILs towards the extraction mechanisms and improved extraction yields are additionally provided. The isolation and recovery procedures of the value-added compounds are ascertained as well as some scattered strategies already reported for the IL solvent recovery and reusability. Finally, a critical analysis on the economic impact *versus* extraction performance of IL-based methodologies was also carried out and is here presented and discussed.

Introduction

In the last decades, the word “green” acquired a new meaning in chemistry-related fields. The introduction of the twelve principles of green chemistry had a major role on the development of “green engineering”¹ and the importance of sustainable development and “green chemistry” changed the way by which academia and industry design chemical processes. In this context, the minimization of the environmental and health impacts of molecular solvents commonly used in industry became a priority. Novel approaches have been proposed addressing the use of safer alternatives with more environmentally friendly characteristics. Some examples include the use of solvents produced from renewable resources, water, supercritical CO₂, and ionic liquids (ILs).²

ILs are salts with melting temperatures below 100 °C – a result of their low-charge density and low symmetry ions.³ These salts are usually composed of a large organic cation and an organic or inorganic anion, and are generally described as “designer solvents” since there is a large degree of cation/anion combinations bestowing them with the possibility of tuning their properties, such as their thermophysical properties, biodegradation ability or toxicological features, as well as their hydrophobicity and solution behaviour.⁴⁻⁷

The first IL, ethylammonium nitrate with a melting point of 12 °C, was synthesized in 1914, when Paul Walden was testing new explosives for the replacement of nitroglycerin.⁸ Later on, in

1934, the first patent regarding the industrial application of ILs in the preparation of cellulose solutions was filled.⁹ During the 2nd World War, further patents involving the use of ILs as mixtures of aluminium chloride (III) and 1-ethylpyridinium bromide for the electrodeposition of aluminium were obtained.^{10,11} Nevertheless, only in the past few years, with the appearance of air- and water-stable ILs, as well as of task-specific compounds, the research on the synthesis of novel ILs and on their possible applications has significantly increased.¹²

Nowadays, amongst the large range of ILs that can be synthesized, the most commonly studied cations are nitrogen-based, namely pyrrolidinium-, imidazolium-, piperidinium-, pyridinium- and quaternary-ammonium, combined with anions such as chloride (Cl⁻), bromide (Br⁻), acetate ([C₁CO₂]⁻), hexafluorophosphate ([PF₆]⁻) and tetrafluoroborate ([BF₄]⁻). However, the development of novel ILs is moving away from the more hydrophobic and fluorinated anions ([PF₆]⁻, [BF₄]⁻, etc.) towards less toxic and biodegradable alternatives, namely derivatives from carboxylic acids and amino-acid-based anions.^{13,14} The search of ILs produced from renewable resources, that are biodegradable and biocompatible, has also been a goal with the synthesis of cholinium- and amino-acid-based cations,¹⁵ and more recently, with the synthesis of two new classes of low-toxicity ILs: imidazolium- and pyridinium-derivatives of mandelic acid.^{16,17} The synthesis of novel biodegradable and low-toxicity ILs has considerably increased in the past few years, and several ILs are already classified as biodegradable (where at least

60 % of the compound is biodegraded within 28 days).¹⁸

Due to their ionic character, most aprotic ILs exhibit unique properties, namely a negligible vapour pressure, low flammability, high thermal and chemical stabilities, broad liquid temperature range, high ionic conductivity, high solvation ability for organic, inorganic and organometallic compounds and improved selectivity.¹⁹⁻²¹ All these features make of them potential alternatives to the volatile organic compounds (VOCs) commonly used in the most diverse applications, namely in biphasic catalysis, in organic synthesis, in polymerization, in separation and extraction processes and in the dissolution of biomaterials.²²⁻²⁶ Actually, ILs are used in organic chemistry (homogeneous catalysis, Heck reaction or Suzuki reaction)²⁷⁻³⁰ along with new materials chemistry (electrolytes for the electrochemical industry and liquid crystals).³¹⁻³⁴ Moreover, ILs also demonstrated a good performance in biocatalysis, while providing a non-denaturing environment for biomolecules and maintaining the protein structure and enzymatic activity.³⁵

Although 100 years have passed since the synthesis of the first IL,⁸ there is still much to explore and to learn with these compounds. The research on their synthesis, characterization and applications is still under continuous development.

ILs solutions as extractive solvents

During the past few years, the discrimination between natural and synthetic products has received an enormous attention, due to an increased demand on the consumption of natural compounds over their synthetic counterparts. The risk of fraud by false declarations regarding the compounds origin has largely increased and led to the establishment of new guidelines by regulatory entities.³⁶ For instance, caffeine-containing drinks are very popular around the world, and recently, the Food and Drug Administration (FDA) regulated that any added caffeine must be labelled on human consumption products owing to possible adulteration and health concerns.³⁶ Another worthy example is the current controversy that exists regarding the consumption/use of natural *versus* synthetic antioxidants.³⁷ Most consumers prefer natural antioxidants since the safety of the synthetic compounds is not fully known.³⁷ Based on these human apprehensions, the extraction of value-added compounds or fine chemicals from natural sources has gained a tremendous importance. Nonetheless, conventional extraction processes still present several drawbacks, such as a low efficiency, non-selectivity, are time-consuming, require a high energetic input, can lead to the degradation of the targeted compounds, among others. Furthermore, traditional methods generally involve the use of large amounts of volatile and often toxic organic solvents leading to inherent environmental concerns. Moreover, the application of hazardous solvents may prevent the high-value chemicals to be used for human consumption.³⁸

In the beginning of the 21st century, with the appearance of air- and water-stable ILs, the research on the development of novel ILs and towards their potential applications increased significantly.¹² A new era on the study of ILs as potential candidates for the extraction of value-added compounds from natural sources has appeared. Their unique properties, which can be tailored, and their ability to solvate a large array of compounds, coupled to the requisite of finding more rentable,

efficient and “greener” solvents are the major reasons behind this trend. The pioneering work foreseeing that goal was published in 2007, by Du et al.³⁹ The authors³⁹ demonstrated the successful application of ILs aqueous solutions in microwave-assisted extraction (MAE) to extract trans-resveratrol from a Chinese traditional medicine herb. After this proof of principle, the number of investigations regarding the use of ILs for the extraction of value-added materials increased significantly.³⁹⁻⁸³ Since 2007 to the end of 2013, 45 articles reporting the application of ILs (either pure or as mixtures with molecular solvents) for the extraction of value-added compounds from natural sources were published (Fig. 1). Most works were carried out with aqueous solutions of ILs (24 articles). Pure ILs (16 articles) and IL-ethanol or IL-methanol mixtures were also addressed although in a scarcer number of reports (5 articles).³⁹⁻⁸³

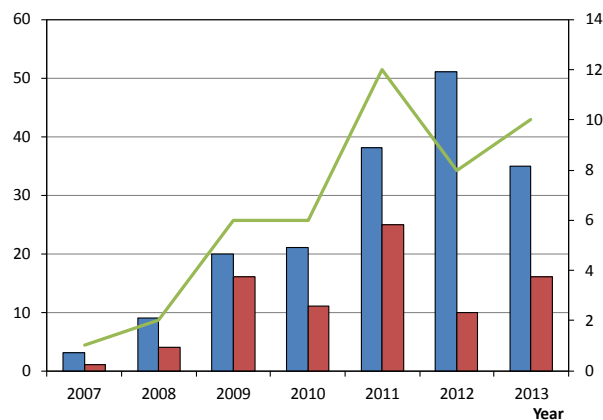


Fig. 1 ILs as solvents for the extraction of value-added compounds. Data from 2007 to 2013: number of articles *per* year (green line, secondary scale); number of ILs studied (blue bars, primary scale); and number of extracted value-added compounds (red bars, primary scale).

The name and acronym of each IL (divided by cation and anion) employed in the extraction of value-added compounds are described in Table 1. The ILs chemical structures are presented in Fig. 2.

Fig. 3 depicts the usage frequency of the distinct cation-anion combinations. The 1-alkyl-3-methylimidazolium, $[C_nC_1im]^+$, is the most investigated cation combined with a large plethora of anions. Although a large number of different cation cores is nowadays available, researchers are still focused on imidazolium-based fluids. Within this group, $[C_4C_1im][BF_4]$, $[C_4C_1im]Cl$ and $[C_4C_1im]Br$ have been the most commonly employed ILs. However, it is already well-established that $[BF_4]$ -based ILs are not water stable even at room temperature,⁸⁴ and some authors conducted their studies with more stable anions, particularly Br^- and Cl^- . Together with these two halogenates, other anions were also studied, such as $[ClO_4]^-$, $[PF_6]^-$, $[HSO_4]^-$ and $[C_nCO_2]^-$. Particularly relevant are the works focused on more biodegradable and less toxic ILs, namely with the application of $[C_4C_1im][Ace]$, $[N_{111}(C_{20}(O)C_{12})]Cl$, $[N_{1100}][N(C_1)_2CO_2]$, $[N_{11(3N)0}][C_2CO_2]$, $[N_{11(2(O)2OH)0}][C_2CO_2]$ and $[N_{111(2OH)}]$ -based ILs in the extraction of antioxidants, polyphenols, saponins, suberin, among others.^{40,43,50,58,63,75-77}

All the investigations reporting the use of ILs, or their solutions, for the extraction of value-added compounds from biomass employed solid-liquid-type extractions (SLE). Some of

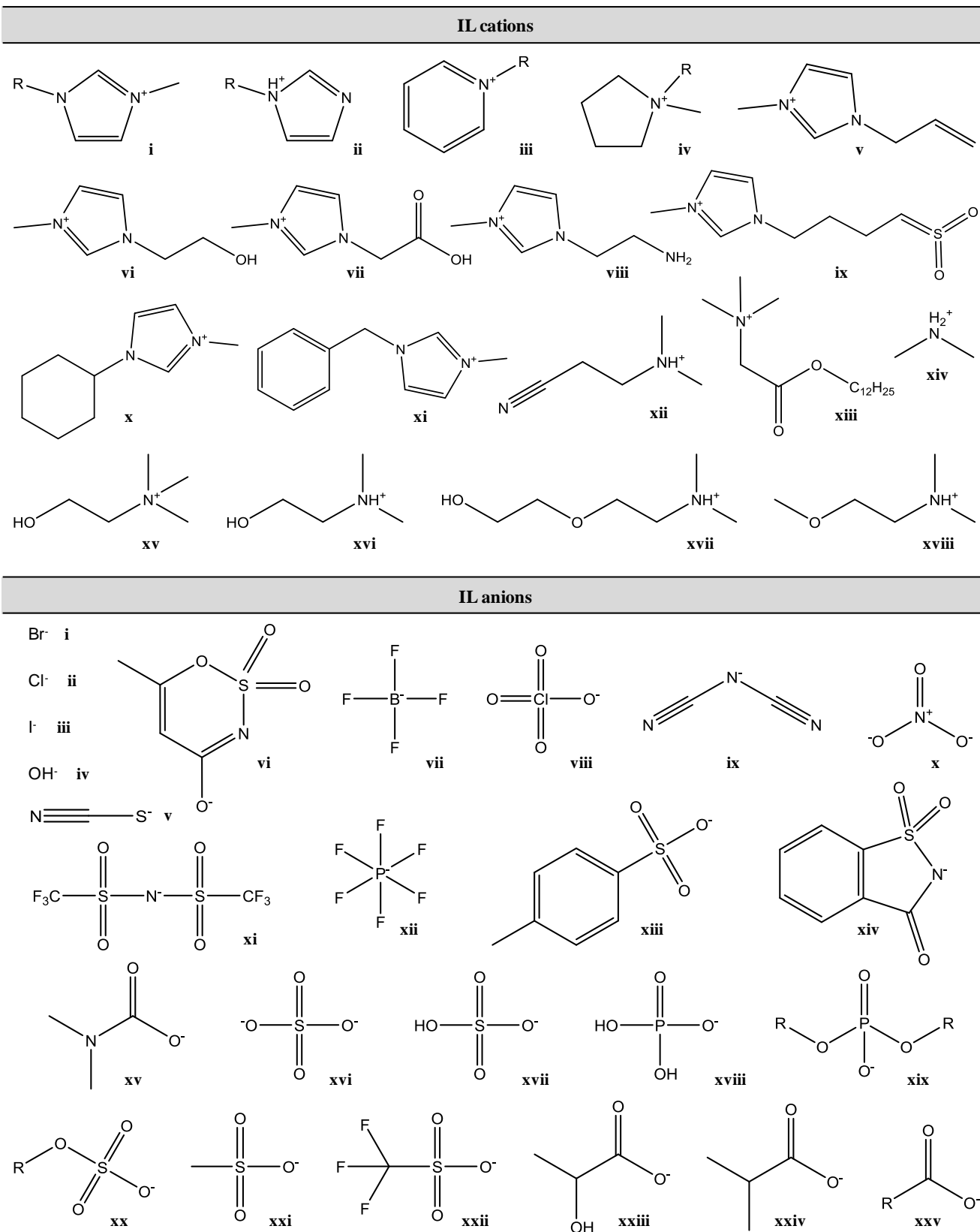
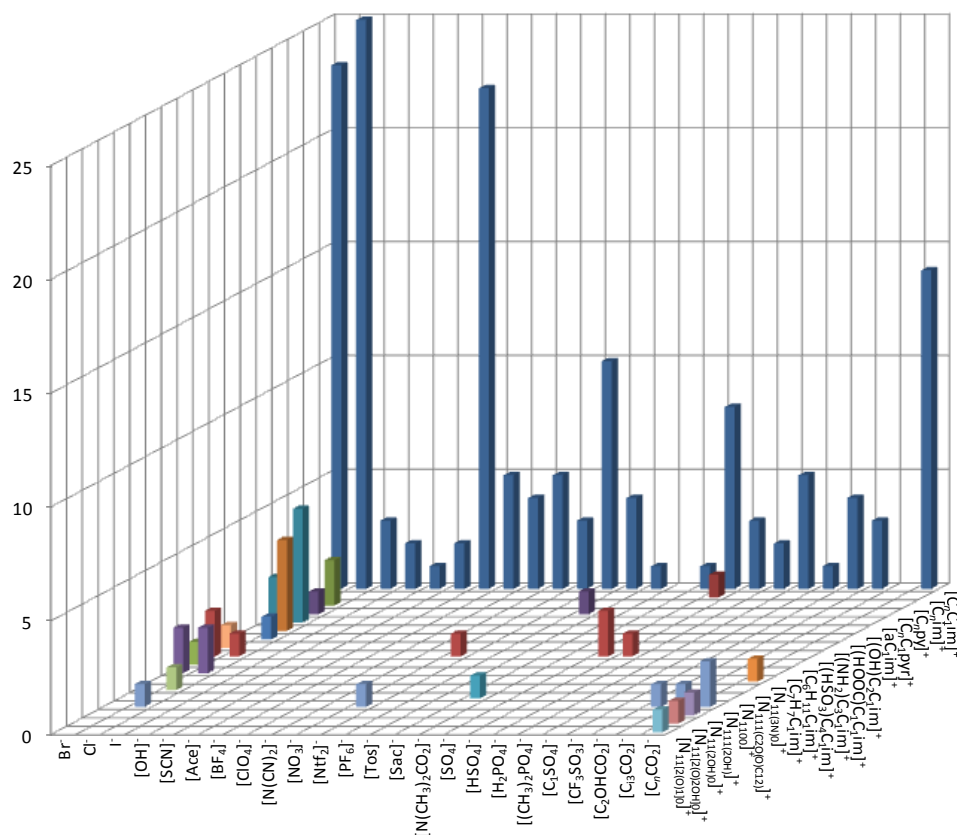


Fig. 2 Chemical structure of each IL cation and anion employed in the extraction of value-added compounds from natural sources. The nomenclature of each ion is presented in Table 1.

Table 1 Name and respective acronym of the cation-anion combinations in ILs.

Cations		Anions	
Name	Acronym	Name	Acronym
i 1-alkyl-3-methylimidazolium	$[C_nC_1im]^+$	i bromide	Br^-
ii 1-alkylimidazolium	$[C_nim]^+$	ii chloride	Cl^-
iii 1-alkylpyridinium	$[C_npy]^+$	iii iodide	I^-
iv 1-alkyl-1-methylpyrrolidinium	$[C_nC_1pyr]^+$	iv hydroxide	$[OH]^-$
v 1-allyl-3-methylimidazolium	$[aC_1im]^+$	v thiocyanate	$[SCN]^-$
vi 1-hydroxyethyl-3-methylimidazolium	$[(OH)C_2C_1im]^+$	vi acesulfamate	$[Ace]^-$
vii 1-carboxymethyl-3-methylimidazolium	$[(HOOC)C_1C_1im]^+$	vii tetrafluoroborate	$[BF_4]^-$
viii 1-propylamine-3-methylimidazolium	$[(NH_2)C_3C_1im]^+$	viii perchlorate	$[ClO_4]^-$
ix 1-(4-sulfonylbutyl)-3-methylimidazolium	$[(HSO_3)C_4C_1im]^+$	ix dicyanamide	$[N(CN)_2]^-$
x 1-cyclohexyl-3-methylimidazolium	$[C_6H_{11}C_1im]^+$	x nitrate	$[NO_3]^-$
xi 1-benzyl-3-methylimidazolium	$[C_7H_7C_1im]^+$	xi bis(trifluoromethylsulfonyl)imide	$[Ntf_2]^-$
xii <i>N,N</i> -dimethyl(cyanoethyl)ammonium	$[N_{11(3N)0}]^+$	xii hexafluorophosphate	$[PF_6]^-$
xiii 2-(dodecyloxy)- <i>N,N,N</i> -trimethyl-2-oxoethanaminium	$[N_{11(C20(O)C12)}]^+$	xiii tosylate	$[Tos]^-$
xiv <i>N,N</i> -dimethylammonium	$[N_{1100}]^+$	xiv saccharinate	$[Sac]^-$
xv Cholinium	$[N_{11(2OH)}]^+$	xv dimethylcarbamate	$[N(C_1)_2CO_2]^-$
xvi <i>N,N</i> -dimethylethanolammonium	$[N_{11(2OH)0}]^+$	xvi sulphate	$[SO_4]^-$
xvii <i>N,N</i> -dimethyl- <i>N</i> -(2-hydroxyethoxyethyl)ammonium	$[N_{11(2(O)2OH)}]^+$	xvii hydrogenosulphate	$[HSO_4]^-$
xviii <i>N,N</i> -dimethyl(2-methoxyethyl)ammonium	$[N_{11(2(O)1)0}]^+$	xviii dihydrogenophosphate	$[H_2PO_4]^-$
		xix dialkylphosphate	$[(C_n)_2PO_4]^-$
		xx alkylsulphate	$[C_nSO_4]^-$
		xxi methylsulfonate	$[C_1SO_3]^-$
		xxii trifluoromethanesulfonate	$[CF_3SO_3]^-$
		xxiii lactate	$[C_2OCO_2]^-$
		xxiv isobutyrate	$[C_3CO_2]^-$
		xxv alkylcarboxylate	$[C_nCO_2]^-$

**Fig. 3** Graphical representation of the available data on ILs as extractive solvents and as function of different ions combinations.

these SLE were coupled to MAE and ultrasound-assisted extraction (UAE) aiming at reaching higher extraction yields, and which embody more than two-thirds of the reported works.³⁹⁻⁸³

Amongst the high-value compounds extracted, alkaloids, flavonoids and terpenoids represent 50 % of all fine chemicals investigated, as depicted in Fig. 4. The extraction of aromatic compounds, which include polycyclic and simple structures, along with phenolic acids, lignans and lipids, corresponds to 28 % of the value-added compounds investigated. Finally, natural mixtures, such as essential oils, suberin and saponins have also been considered (11 %). All these natural compounds were extracted from terrestrial and aquatic vegetable sources.^{39-58,60-83} Nevertheless, it should be also remarked the extraction of astaxanthin from shrimp wastes, the only work reported with non-vegetal matrices.⁵⁹

The following discussion is divided by different sections regarding independent natural compounds families, namely alkaloids, flavonoids, terpenoids, aromatic and mixtures of value-added compounds between others. The extraction of lipids from aquatic biomass is also considered, although in a more simplistic analysis. The extraction processes applied, as well as the optimization of the extraction conditions – selection of IL, IL concentration (when applicable), temperature, pH, solid-liquid ratio, ultrasonic/microwave power (when used), are also presented and discussed. Finally, the obtained results, in what concerns the extraction efficiencies and purification factors, are further outlined and discussed.

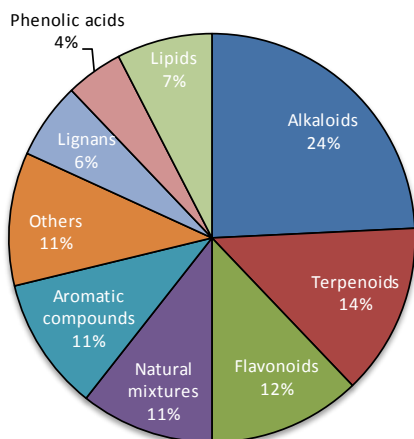


Fig. 4 Fraction of each family of natural compounds extracted from natural sources using ILs or ILs solutions.

Alkaloids

Alkaloids are amongst the most important chemical compounds present in plants. Most alkaloids contain one or more carbon-rings, usually with basic nitrogen atoms, and some examples, such as atropine, nicotine and morphine are derived from amino acids. The position of the nitrogen atom in the carbon ring varies between different alkaloids and defines their properties.⁸⁵ Some examples of alkaloids usually found in biomass are depicted in Fig. 5.

The great interest on alkaloids is related with the effects that they exert on humans. Some of them, such as morphine, codeine

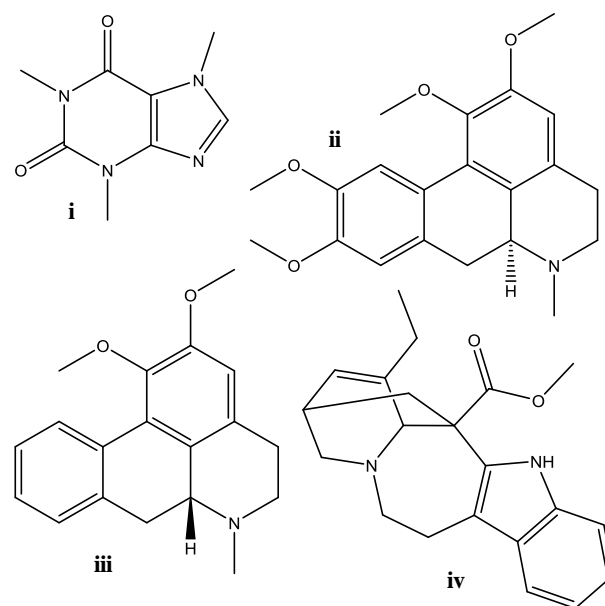


Fig. 5 Chemical structure of common alkaloids: (i) caffeine; (ii) glaucine; (iii) nuciferin; (iv) catharanthine.

and other opioids display structural similarities with neurotransmitters of the human central nervous system and are used as powerful analgesics. Other examples display pharmacological activities, namely antifungal, antidiarrheal and anti-inflammatory characteristics.⁸⁶⁻⁸⁸ Some alkaloids can also cause hallucinogenic effects and are used as psychoactive drugs, such as cocaine.⁸⁹

Heating reflux extraction, soxhlet extraction or maceration at room temperature are the common methods used for the extraction of alkaloids from biomass.⁹⁰ However, these procedures are laborious, time- and energy-consuming, and sometimes require complex equipment and the use of toxic VOCs.⁴¹ Hence, the development of alternative and novel methods for the alkaloids extraction from biomass, and respective recovery, still remains a crucial challenge. To overcome these drawbacks, several researchers have turned to ILs and their solutions to efficiently and selectively extract alkaloids from natural sources.⁴⁰⁻⁴⁹

All the alkaloids extracted from natural sources by the application of ILs solutions are described in Table 2. Amongst the 16 alkaloids investigated, the alkaloids present in the leaves of *Nelumbo nucifera* were the most studied due the importance of this medicinal plant.^{48,49} IL-based UAE is the preferred extraction technique and IL aqueous solutions were always employed.⁴⁰⁻⁴⁹

The use of aqueous solutions of ILs leads to foremost advantages since it reduces the overall viscosity of the extraction solvent, *i.e.*, the high viscosity of most ILs is overwhelm by their mixtures with a low viscous fluid such as water, and thus enhances the mass transfer and reduces energy consumptions. In addition, a much greener and low cost solvent – water – is introduced while increasing the extraction selectivity of the target high-value substances as discussed thereafter. Aqueous solutions also allow the use of high-melting temperature ILs in extraction processes carried out at temperatures close to room temperature. Curiously, for the extraction of alkaloids, mixtures of ILs and molecular organic solvents were never employed. The

main reason for such a decision must rely on the relative polarity and high affinity/solubility of most alkaloids for/in water.

In 2008, for the first time, and again in 2010, Pan and co-workers^{48,49} introduced IL-based MAE for the extraction of alkaloids (isoliensinine, liensinine, neferine, nuciferine, *n*-nornuciferine and *o*-nornuciferine) from *Nelumbo nucifera*. It should be remarked that these works,^{48,49} although using MAE, can be considered a SLE process. Heating reflux extraction is the commonly technique applied to extract these alkaloids.⁹⁰⁻⁹⁵ With the goal of developing a rapid, effective and more environmentally friendly extraction method, Pan and co-workers^{48,49} employed aqueous solutions of imidazolium-based ILs. As a first approach, the authors^{48,49} studied the effect of the IL anion on the extraction efficiencies. With a fixed [C₄C₁im]⁺ cation coupled to the anions Cl⁻, Br⁻, [BF₄]⁻ and [PF₆]⁻ it was observed that [C₄C₁im][BF₄] is the most efficient IL for the extraction of isoliensinine, liensinine and neferine.⁴⁸ On the other hand, [C₄C₁im]Br displayed the best performance on the extraction of nuciferine, *n*-nornuciferine and *o*-nornuciferine. The authors^{48,49} also concluded that the alkaloids extraction efficiency increases with the IL cation alkyl side chain length. However, sufficiently long aliphatic moieties, for instance increasing the longest alkyl chain length at the imidazolium cation from hexyl to octyl, lead to a drastic decrease on the alkaloids extraction. The authors explained this pattern based on the miscibility between the different ILs and water.^{48,49} However, the self-aggregation of long alkyl side chain ILs in aqueous media cannot be discarded.⁹⁶

Table 2 List of alkaloids extracted from natural sources using ILs or ILs solutions (the molecular solvent is presented between parentheses) and different extraction techniques employed.

Value-added compound	Natural source	Technique	IL
Glaucine	<i>Glaucium flavum</i> (papaveraceae)		[C ₄ C ₁ im][Ace], [C ₁₀ C ₁ im][Ace], [C ₆ C ₁ im][Ace], [C ₈ C ₁ im][Ace], [C ₄ C ₁ im][Sac], [C ₄ C ₁ im]Br, [C ₄ C ₁ im]Cl (water) ^{40,41}
Caffeine	<i>Paullinia cupana</i> (guaraná)	SLE	[C ₂ C ₁ im]Cl, [C ₂ C ₁ im][C ₁ CO ₂], [C ₄ C ₁ im]Cl, [C ₄ C ₁ im][Tos], [C ₄ C ₁ pyr][Tos], [(OH)C ₂ C ₁ im]Cl (water) ⁴²
Piperine	<i>Piper nigrum</i> (white and black pepper)		[C ₁₀ C ₁ im]Cl, [C ₁₂ C ₁ im]Cl, [C ₁₂ C ₁ im]Br, [C ₁₂ C ₁ im][CF ₃ SO ₃], [C ₁₂ C ₁ im][C ₁ CO ₂], [C ₁₂ C ₁ im][N(CN) ₂], [C ₁₄ C ₁ im]Cl, [N ₁₁₁₁ (C ₂₀ O ₂ C ₁₂)Cl (water) ⁴³
10-Hydroxycamptothecin	<i>Camptotheca acuminata</i>		[C ₄ C ₁ im][BF ₄], [C ₄ C ₁ im][H ₂ PO ₄], [C ₄ C ₁ im][PF ₆], [C ₄ C ₁ im]Br, [(HSO ₃)C ₄ C ₁ im]Br, [C ₆ C ₁ im][BF ₄] (water) ⁴⁴
Camptothecin			[aC ₁ im]Br, [C ₇ H ₇ C ₁ im]Br, [C ₂ C ₁ im]Br, [C ₃ C ₁ im]Br, [C ₄ C ₁ im][BF ₄], [C ₄ C ₁ im][ClO ₄], [C ₄ C ₁ im][HSO ₄], [C ₄ C ₁ im][NO ₃], [C ₄ C ₁ im]Br, [C ₄ C ₁ im]Cl, [C ₆ C ₁ im]Br, [C ₈ C ₁ im]Br, [C ₆ H ₁₁ C ₁ im]Br (water) ⁴⁵
Catharanthine		UAE	[aC ₁ im]Br, [C ₂ C ₁ im]Br, [C ₄ C ₁ im][BF ₄], [C ₄ C ₁ im][ClO ₄], [C ₄ C ₁ im][HSO ₄], [C ₄ C ₁ im][NO ₃], [C ₄ C ₁ im][Tos], [C ₄ C ₁ im]Br, [C ₄ C ₁ im]Cl, [C ₄ C ₁ im]I, [C ₆ C ₁ im]Br, [C ₈ C ₁ im]Br (water) ⁴⁶
Vinblastine		<i>Catharanthus roseus</i>	
Vindoline			
Fangchinoline	<i>Stephaniae tetrandrae</i>		[C ₄ C ₁ im][BF ₄] (water) ⁴⁷
Tetrandrine			
Isoliensinine	<i>Nelumbo nucifera</i> (lotus leaf)		[C ₂ C ₁ im][BF ₄], [C ₄ C ₁ im][BF ₄], [C ₄ C ₁ im][PF ₆], [C ₄ C ₁ im]Br, [C ₄ C ₁ im]Cl, [C ₆ C ₁ im][BF ₄], [C ₈ C ₁ im][BF ₄] (water) ⁴⁸
Liensinine			
Neferine		MAE	
Nuciferine			
<i>N</i> -Nornuciferine			
<i>O</i> -Nornuciferine			

The authors^{48,49} also optimized three operational conditions: irradiation power, extraction time and solid-liquid ratio (biomass-solvent ratio). It was found that the irradiation power has no significant influence on the extraction efficiency. Conversely, it was observed a significant increase on the extraction efficiency in short periods of time (0-1 min), whereas for longer times it reaches a plateau. This plateau is usually a result of the solvent saturation or an indication of the complete extraction. Finally, a decrease on the solid-liquid ratio led to the increase on the extraction efficiency of alkaloids.^{48,49}

Pan and co-workers^{48,49} also compared IL-based MAE with regular MAE and conventional heating reflux extraction methodologies. IL-based MAE led to higher extraction efficiencies (enhancement of 0.9 – 50.0 %) and strongly reduced the extraction time (from 2h to 90s). The combination of ILs aqueous solutions and MAE results, thus, in a simple, fast and efficient extraction strategy.^{48,49}

One of the most recent areas of SLE in which ILs are applied consists on the use of UAE. In 2009, Cao et al.⁴⁴ reported the pioneering work on the development of IL-based UAE for the extraction of piperine from *Piper nigrum* - unripe fruit seeds (white pepper). After this proof of principle, several works then appeared regarding the use of IL-based UAE in the extraction of value-added compounds. Ma et al.⁴⁵ reported the extraction of 10-hydroxycamptothecin and camptothecin from *Camptotheca acuminata*; Yang et al.⁴⁶ studied the extraction of vindoline, catharanthine and vinblastine from *Catharanthus roseus*; and

Zhang et al.⁴⁷ used IL-based UAE to recover fangchinoline and tetrandrine from *Stephaniae tetrandrae*. In these works⁴⁴⁻⁴⁷ a large number of ILs was investigated allowing the inspection on the effect of the IL anion and cation alkyl side chain length (cf. Table 2).⁴⁴⁻⁴⁷ The authors⁴⁴⁻⁴⁷ found that the alkaloids extraction is mainly IL anion-dependent, and which is in accordance with the results reported by Pan and co-workers.^{48,49} In general, more hydrophilic ILs, such as [C₄C₁im]Br and [C₄C₁im]Cl, are better extractive solvents. However, the effect of the IL cation cannot be discarded and needs to be taken into consideration. Ma et al.⁴⁵ and Yang et al.⁴⁶ reported that the alkaloids extraction efficiency increases with the cation alkyl side chain length. It was also observed that ILs with an allyl group at the cation lead to an improvement on the extraction performance.^{45,46} Moreover, for the same number of carbon atoms, comparing an aliphatic and linear moiety with a cyclic group, [C₆C₁im]Br and [C₆H₁₁C₁im]Br, there are also relevant differences on their extraction abilities. The extraction efficiencies are substantially higher with the former IL meaning that a linear alkyl chain in [C₆C₁im]Br is more favourable for the alkaloids extraction.⁴⁵

In general, all authors⁴⁴⁻⁴⁷ observed a maximum on the extraction efficiency as a function of the IL concentration. It is consensual that the decrease on the extraction efficiency observed at higher IL concentrations is a main result of the increase of the solution viscosity which hinders an efficient solvent penetration into the plant tissues.⁴⁴⁻⁴⁷

The ultrasonic power is a driving force for the complete IL dispersion and access into the natural matrix. The higher the ultrasonic power, the better is the extraction efficiency of alkaloids.⁴⁴⁻⁴⁷ Furthermore, in all works, it was observed an increase in the alkaloids extraction with the increase of the solid-liquid ratio.⁴⁴⁻⁴⁶ This trend is similar to that described before for the MAE-based processes.^{48,49}

Although most alkaloids present proton donor and acceptor sites (Fig. 5) and therefore can suffer speciation, Zhang et al.⁴⁷ were the only research group which evaluated the effect of the pH on the extraction efficiencies of alkaloids, namely fangchinoline and tetrandrine. The authors⁴⁷ observed that the extraction efficiencies of alkaloids increased up to 100 %, as the pH increases from 0.2 to 9.8, and then decrease up to a pH value of 13.8. Although not discussed in detail by the authors⁴⁷, this dependence of the extraction efficiencies with the pH of the aqueous medium is connected to the alkaloids speciation. The acidic dissociation constants, pK_a, for fangchinoline, are 8.4 and 9.2, whereas for tetrandrine it is 8.4.⁹⁷ Below a pH of 8.4, both alkaloids are in their neutral form, while above 9.2, fangchinoline is mainly present as a negatively charged species. In this context, it seems that the alkaloids are better extracted by IL aqueous solutions when in a non-charged form. Higher pH values also lead to the alkalization of the starch contained in the dried roots of *Stephaniae tetrandrae* and also support the observed decrease on the extraction efficiencies, as highlighted by the authors.⁴⁷

Yang et al.⁴⁶ were the only researchers evaluating the effect of the soaking time whereas a significant increase on the alkaloids extraction efficiencies from *Catharanthus roseu* was observed.⁴⁶ This effect was attributed to an enhanced diffusion of the solvent into the cellular structure allowing for an improved solubilisation of the alkaloids.⁴⁶ Zu and co-workers^{45,46} also investigated the

number of extraction cycles. In both reports it was concluded that it is possible to obtain a cumulative extraction efficiency up to 100 % within 4 extraction cycles.^{45,46}

Based on the results previously presented,⁴⁴⁻⁴⁷ IL-based UAE appears as an alternative technique for the extraction of alkaloids from natural sources, with extraction efficiencies up to 100 %, and with a reduced extraction time when compared with conventional heating reflux extraction and regular UAE techniques.

Besides the recurrent use of ultrasonic power and microwave irradiation,⁴⁴⁻⁴⁹ only recently, three research groups suggested the use of ILs aqueous solutions as extractive solvents in simple SLE approaches, namely in the extraction of glaucine from *Glaucium flavum*,^{40,41} of caffeine from *Paullinia cupana* (guaraná seeds),⁴² and of piperine from *Piper nigrum* (black pepper) - cooked and dried unripe fruit.⁴³ These simpler SLE extraction techniques avoid the use of specific and more expensive equipment such as those required in UAE- and MAE-based processes. Contrarily to the common sense it seems that the research on the extraction of alkaloids using IL-based solvents started with more complex approaches.

Bogdanov et al.⁴¹ studied the effect of the IL anion (Cl⁻, Br⁻, [Ace⁻] and [Sac⁻]), the cation alkyl side chain length in the [C_nC₁im]⁺ series, the concentration of the IL in aqueous solutions, the extraction time and the biomass-solvent ratio. As previously shown for other alkaloids,^{44-46,48,49} the extraction efficiency for glaucine is strongly IL anion-dependent. However, when comparing the extraction efficiencies obtained with aqueous solutions of [C_nC₁im][Ace⁻] ILs (85 %) or potassium acesulfamate (< 50 %), as well as those obtained with pure water (40 %), it is evident the role played by the organic imidazolium cation on the overall extractive process.⁴¹ Therefore, in addition to the effect of the IL into the destruction of the biomass structure, that we assume that is highly anion-dependent and as supported by the well-known studies on the dissolution of cellulose,²⁵ the IL cation also plays a fundamental role. ILs composed of cations with an electron-rich aromatic π -system, such as an imidazolium, can establish strong interactions with polarizable solute molecules, such as alkaloids. Hence, these inherent non-covalent interactions seem to control the affinity and selectivity displayed by ILs for the extraction of alkaloids. Although these assumptions seem to be valid, more studies are needed at this point. The summary provided in Table 2 reveals that besides two isolated experiments with a pyrrolidinium- and an ammonium-based IL, all the remaining studies were accomplished with imidazolium-based fluids. Actually, additional extraction studies with quaternary ammonium-, and in particular with cholinium-based ILs due to their more benign character, quaternary phosphonium-, guanidinium-, sulfonium-, and piperidinium-based ILs are of crucial importance to clearly identify the IL anion and cation impact through the extraction mechanism.

The extraction efficiencies of glaucine also increase with the IL concentration, with a maximum of 99 % attained at 2 M of IL, and with the solvent volume (IL aqueous solutions).⁴¹ Bogdanov et al.⁴¹ also observed that for both solvents, water and [C₄C₁im][Ace⁻] aqueous solutions, at 80 °C, it was possible to attain the same extraction yield achieved at room temperature, yet, with a significant reduction in the extraction time (from 12h

to 1h). As suggested by the authors⁴¹ this effect seems to be related with the effect of temperature on the solubilisation ability inside the solid matrix, with the increase of the diffusion coefficient and decrease of the IL solution viscosity. Sonication was also tested although the obtained results were not promising.⁴¹

Later, Svinyarov and co-workers⁴⁰ reported a more detailed work on the kinetics, modelling and mechanism of glaucine extraction from *Glaucium flavum*. In this work, the temperature dependence of the kinetics of both methanol and [C₄C₁im][Ace]-supported extractions was measured and a comparative analysis on the extraction solvent was performed.⁴⁰ The fitting of the experimental data disclosed that, in these examples, the extraction process follows a second-order kinetics.⁴⁰ A plausible extraction mechanism was also proposed: the apparent kinetics and high yields obtained with ILs were attributed to the cell walls modification by hydrogen-bonding interactions between both ions of [C₄C₁im][Ace] and cellulose, which further results in the plant tissues disruption.⁴⁰

Cláudio et al.⁴² investigated the selective extraction of caffeine from guaraná seeds. NaCl or [C₄C₁im]Cl aqueous solutions were initially used allowing to conclude that the ionic strength is a not relevant factor regarding the caffeine extraction.⁴² Since both salts are chloride-based, these results are also an indication on a significant role exhibited by the IL organic cation as discussed before. Simultaneously, the IL concentration effect was studied and the best results were achieved with the higher concentrations of IL (2.5-3.0 M).⁴² At these concentrations, the still low viscosity of the IL aqueous solutions allows a good penetration of the solvent into the sample matrix and a rapid mass transfer of caffeine into the liquid phase (Fig. 6). The IL chemical structure was additionally analysed through the application of six ILs: [C₂C₁im]Cl, [C₂C₁im][C₁CO₂], [C₄C₁im]Cl, [C₄C₁im][Tos], [C₄C₁pyr]Cl and [(OH)C₂C₁im]Cl. All the studied ILs lead to a similar percentage of extracted caffeine.⁴² Moreover, since [C₄C₁im]Cl and [C₄C₁pyr]Cl showed similar extraction profiles, the authors concluded that the presence of an aromatic ring in the cation had no significant effect on the extraction.⁴² Nevertheless, it should be remarked that this is one of the few works where a non-aromatic IL was employed and certainly more works are needed to support this conclusion. Overall, and according to previous discussions, the authors⁴² suggested that the extraction mechanism is mainly governed by the IL effect upon the biomass structure. Scanning electron microscopy (SEM) images of guaraná grinded seeds after the extraction with water and with an IL are depicted in Fig. 6. In both examples, broken cells are visible; however, the ratio of broken to intact cells is considerably higher for the guaraná samples after the extraction with [C₄C₁im]Cl.⁴²

Cellulose is the main constituent of vegetable cell walls and the ability of some ILs to dissolve cellulose is well-known.²⁵ In addition, it is already established that the solvation of cellulose by ILs is driven by the hydrogen-bonding network established between the IL anion and the -OH groups of the polymer.^{98,99} Therefore, ILs such as [C_nC₁im]Cl and [C_nC₁im][C_nCO₂], composed of anions with a high aptitude to accept protons or with a high hydrogen-bond basicity, are the most effective in the biomass dissolution^{25,98,99} and further lead to improved extraction

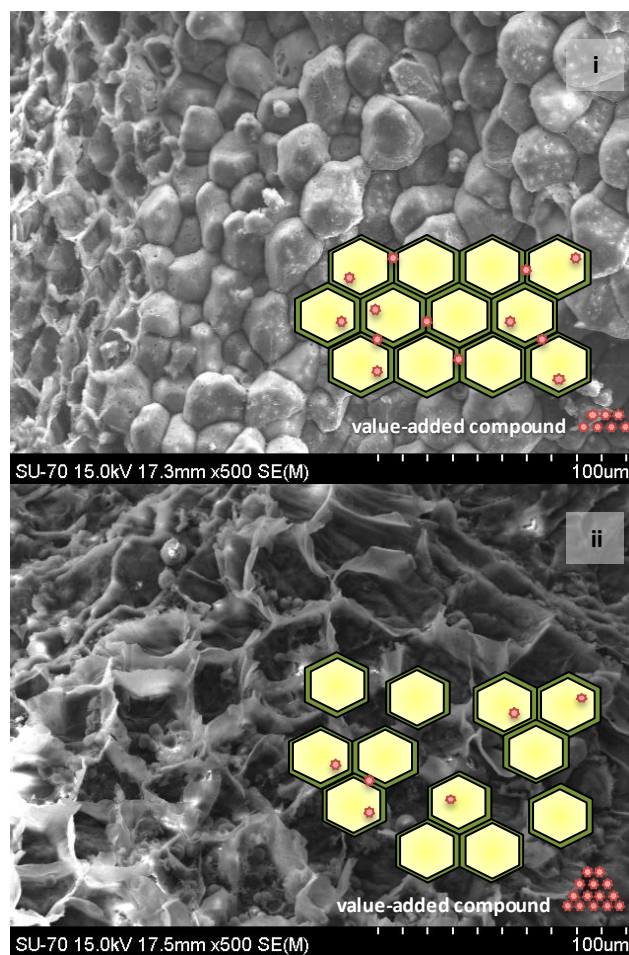


Fig. 6 SEM pictures and schematic representation of the extraction mechanism of caffeine from guaraná seeds with (i) water and (ii) an aqueous solution of [C₄C₁im]Cl. Adapted from Cláudio et al.⁴² and Zirbs et al.⁶⁷

performances.^{40-42,44-49}

The effect of the particles size on the caffeine extraction was also ascertained and it was observed that smaller particles of guaraná seeds lead to higher extraction yields.⁴² Additional operational conditions, such as the IL concentration, the contact time, the solid-liquid ratio and the temperature were also optimized by a response surface methodology. At the optimum conditions (time = 30 min; temperature = 70 °C; aqueous solution of [C₄C₁im]Cl at 2.34 M; solid-liquid ratio = 0.1) the extraction yields of caffeine (weight of caffeine *per* weight of guaraná seeds) were 9.4 wt %.⁴² These values are substantially higher than those observed with a typical soxhlet extraction using dichloromethane (maximum extraction yield of 4.30 wt % for 270 min).⁴² The extraction time and the process temperature were greatly reduced compared to conventional methods which, coupled to the high extraction yields observed, make the proposed extraction technique promising for large-scale applications.

Bica and co-workers⁴³ have taken into account the aggregation behaviour of long alkyl side chain ILs in aqueous media to extract piperine from black pepper by a SLE approach. This work⁴³ represents one of the most complete studies on the effect of the size of the ILs aliphatic moieties. Several long alkyl side

chain $[C_nC_1im]$ -based ILs were studied (with $n = 10, 12$ and 14). Aiming at overcoming the non-negligible toxicity displayed by ILs with long aliphatic tails, the authors also investigated a new, biodegradable, betain-derived IL ($[N_{111}(C_{20}(O)C_{12})Cl]$).⁴³ The IL anion effect on the extraction efficiency of piperine was also ascertained by the combination of $[C_nC_1im]^+$ with the anions Cl^- , Br^- , $[CF_3SO_3]^-$, $[C_1CO_2]^-$ and $[N(CN)_2]^-$.⁴³

The operational conditions were initially optimized to achieve a good compromise between the time demand and the extraction yield. The increase of the solid-liquid ratio introduced some mixing problems with a consequent decrease on the extraction efficiency.⁴³ After the previous optimization tests, the influence of the IL concentration was analysed and interesting results were obtained: for IL concentrations below the critical micellar concentration (CMC) only small amounts of piperine (< 0.2 wt %) are extracted; yet, when the IL concentration is higher than the respective CMC, the extraction yield of piperine significantly increases (~ 4.0 wt % with a 100 mM IL solution). This behaviour was observed with all $[C_nC_1im]Cl$ -based ILs, as well as with $[N_{111}(C_{20}(O)C_{12})Cl]$. Indeed, this biodegradable IL revealed a high-performance on the extraction of piperine and can be used as a potential solvent when greener and large-scale applications are envisaged. Concerning the IL anion effect, it was observed only a slightly influence through the piperine extraction. Albeit the IL anions investigated present a small effect on the ILs surface-activity, these are composed of anions that can affect the biomass morphology as discussed above. Rössmann et al.⁴³ also identified, by electron microscopy, an increase on the ratio of broken cells to intact cells in black pepper samples in the presence of IL aqueous solutions.⁴³ These results, in agreement with the previous discussion, reveal that it is not necessary to completely dissolve the biomass matrix – and which is prevented by the presence of water – to obtain an efficient extraction of the value-added compounds. Only a partial destruction of the biomass primary structure is required for an improved extraction. At this point, it can be concluded that ILs destroy the biomass structure and that when ILs with long alkyl chains are used for the extraction of alkaloids, the formation of aggregates above the CMC seems to govern the extraction mechanism and selectivity. Nevertheless,

more studies involving surface-active ILs at concentrations above their CMC are of utmost importance.

The authors⁴³ also compared the results obtained on the extraction of piperine using IL-based aqueous solutions with conventional organic solvents, such as chloroform, toluene and methanol.⁴³ The authors concluded that the micelle-based solutions of $[C_nC_1im]$ -based ILs are an improved alternative to volatile solvents.⁴³

Flavonoids

Flavonoids are a large group of natural compounds (responsible for colouring) which can be found in fruits, vegetables, roots, flowers, tea, algae, among others. Flavonoids present a common central heterocyclic ring (Fig. 7) and are divided into various classes based on their molecular structure: flavones, flavanones, catechins, anthocyanins, etc.¹⁰⁰ These compounds lead to some benefits in human health due to their anti-atherosclerotic, anti-inflammatory, antitumor, anti-thrombogenic, anti-osteoporotic and antiviral properties.¹⁰¹

All the flavonoids extracted from natural sources by the application of ILs are described in Table 3. A total of 8 flavonoids, 17 ILs and 3 different separation processes were studied. The most investigated IL was $[C_4C_1im][BF_4]$ in aqueous solution. An isolated research work where a pure IL was employed was also reported.⁵⁰

(+)-Catechin is a flavonoid with important human health benefits, also known as a tannin, that can be used for the processing of animal hide into leather.⁵⁰ Concerning the application of tannins in the treatment of leather, the use of chromium (Cr (III)) tannins is the most popular approach. However, this process and its variants display major drawbacks to the environment and for those who come into contact with manufactured leather pieces.^{102,103} These facts have resulted in the banning of this method in the European Union (EU) as well as in the recommendation, by the United Nations Industrial Development Organization (UNIDO), that chromium tanning should be avoided and vegetable tannins should be used as a major alternative.¹⁰⁴

Table 3 List of flavonoids extracted from natural sources using ILs or ILs solutions (the molecular solvent is presented between parentheses) and different extraction techniques employed.

Value-added compound	Natural source	Technique	IL
(+)-Catechin	<i>Acacia catechu</i> (catechu) and <i>Terminalia chebula</i> (myrobolan)	SLE	$[N_{1100}][N(C_1)_2CO_2]$ (pure IL) ⁵⁰
Iristectorin A			
Iristectorin B	<i>Iris tectorum</i>	UAE	$[C_4C_1im][BF_4]$, $[C_6C_1im]Br$, $[C_8C_1im]Br$ (water) ⁵¹
Tectoridin			
Kaempferol			$[C_2C_1im]Br$, $[C_4C_1im][BF_4]$, $[C_4C_1im][H_2PO_4]$, $[C_4C_1im][HSO_4]$, $[C_4C_1im][PF_6]$, $[C_4C_1im]_2[SO_4]$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$, $[C_6C_1im]Br$, $[(HOOC)C_1C_1im]Cl$ (water) ⁵²
Myricetin	<i>Bauhinia championii</i>		
Quercetin	<i>Psidium guajava</i> (guava) and <i>Smilax china</i>	MAE	$[C_2C_1im][BF_4]$, $[C_2C_1im]Br$, $[C_4C_1im][BF_4]$, $[C_4C_1im][C_1SO_4]$, $[C_4C_1im][H_2PO_4]$, $[C_4C_1im][N(CN)_2]$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$, $[C_4py]Cl$, $[C_6C_1im]Br$ (water) ⁵³
Rutin	<i>Saururus chinensis</i> and <i>Flos sophorae</i>		$[C_4C_1im][BF_4]$, $[C_4C_1im][Tos]$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$ (water) ⁵⁴

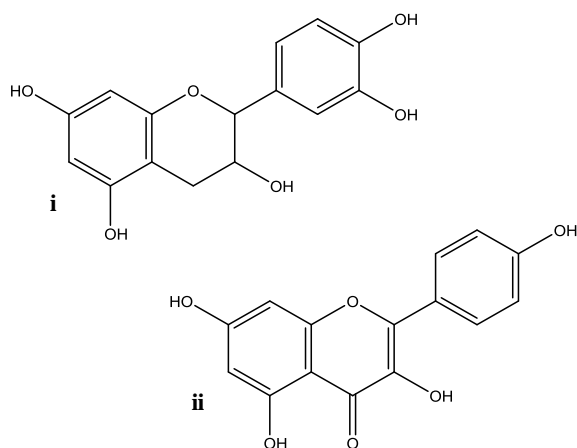


Fig. 7 Chemical structure of some flavonoids: (i) (+)-catechin; (ii) kaempferol.

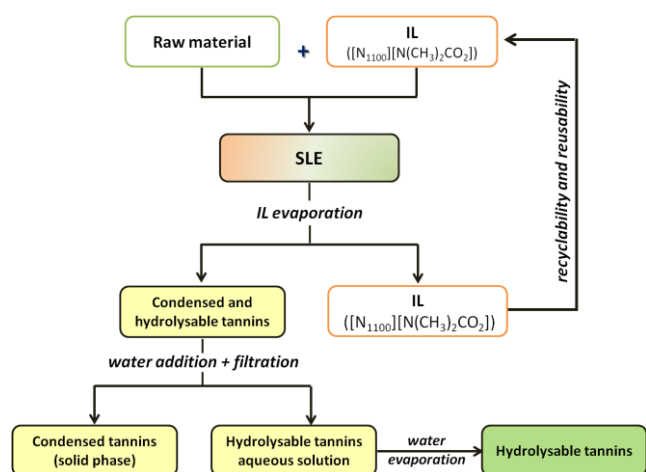


Fig. 8 Flowchart of the process used to extract vegetable tannins.⁵⁰

The conventional methods applied for the extraction of hydrolysable vegetable tannins require relatively harsh conditions, such as high temperatures (70 °C) and high solvent volumes. Furthermore, counter-current techniques are usually employed and yet with poor extraction efficiencies.¹⁰⁵ For the effective use of tannins, it is thus necessary to find an alternative and more effective extraction route. Within this perspective, Chowdhury et al.⁵⁰ have used a protic and distillable IL ($[N_{1100}][N(C_1)_2CO_2]$), at room temperature, to improve the extraction of tannins from *Acacia catechu* (catechu) and *Terminalia chebula* (myrobolan). $[N_{1100}][N(C_1)_2CO_2]$ is formed by combining CO_2 and dimethylamine, in a 1:2 ratio, and can be distilled at around 45 °C. (+)-Catechin, as well as others tannins, such as gallic acid, ellagic acid and pyrocatechol (that also belong to the phenolic acids or antioxidants group) were extracted with $[N_{1100}][N(C_1)_2CO_2]$ by a simple SLE process.⁵⁰ The extraction method applied is summarized in Fig. 8. Certainly, the suggested process is more energetically efficient since the target materials are dissolved into the IL at room temperature. After the extraction procedure, the mixture was filtered and the $[N_{1100}][N(C_1)_2CO_2]$ was recovered.⁵⁰ The results obtained revealed high extraction efficiencies for both catechu (85 %) and myrobolan (75 %). The extraction efficiencies obtained at the same conditions with water are 64 % and 52 %, respectively.⁵⁰ These results clearly support

the high ability of the protic IL to enhance the extraction yields either by its high solvation capacity towards phenolic components or by the capacity that the IL presents in deprotonating them as a part of the dissolution mechanism. The authors⁵⁰ suggested that tannins are essentially extracted into the IL medium in their conjugated base form whereas the IL was recovered as a dimethylammonium salt.⁵⁰ It is also relevant to remark that a microbial assay was performed and that in the samples extracted from myrobolan no contamination was found.⁵⁰ Moreover, it was verified that the recovered IL did not show any fungal growth unlike what usually happens with the water-extraction process.⁵⁰

Most works have been focused on imidazolium-based fluids, and the work published by Chowdhury et al.⁵⁰ represents a strong contribution on the exploitation of alternative ILs. The protic IL used further allows its recovery and reusability by distillation as it will be discussed later. Although the non-volatile nature (and the consequent no contamination of the atmosphere) of the IL is lost, it should be remarked that its low vapour pressure, allied to a proper manipulation and design of the extraction process, as well as the easy IL recovery, can bring significant improvements on the process footprint reduction through the environment.

Rutin is present in the *Saururus chinensis* and *Flos sophorae*, two Chinese medicinal plants, and heating reflux extraction is commonly used for its extraction. Zeng et al.⁵⁴ studied the application of IL-based MAE for the extraction of rutin from these two natural sources. Other authors^{52,53} also employed IL-based MAE for the extraction of additional flavonoids. Du et al.⁵³ reported the application of IL-based MAE for the extraction of a series of polyphenolic compounds, including the flavonoid quercetin from *Smilax china*, whereas Xu et al.⁵² applied the same technique for the extraction of kaempferol, myricetin and quercetin from *Bauhinia championii*.

ILs present a high solvation ability and can efficiently absorb microwave energy - one of the major reasons behind their enhanced extraction yields when coupled to MAE. All authors⁵²⁻⁵⁴ found that the flavonoids extraction is anion-dependent, and which is in agreement with the results discussed before for the extraction of alkaloids. Both type of solutes (*cf.* Figs. 5 and 7) present several -OH groups and aromatic rings and are thus strongly solvated by ILs through the formation of hydrogen-bonds with the IL anions (often strong hydrogen-bond acceptors). The ILs $[C_4C_1im]Br$ and $[C_4C_1im][Tos]$ displayed the best extraction yields for rutin,⁵⁴ with values close to those obtained with methanol. However, considering the methanol volatility, flammability and human and environmental negative effects, IL aqueous solutions can be envisaged as “greener” alternatives.

$[PF_6]$ -based ILs led to lower extraction efficiencies of flavonoids from *Bauhinia championii*, while ILs with the anion Br^- result in improved extractions.⁵² On the other hand, the highest extraction yields of quercetin from *Psidium guajava* leaves and *Smilax china* tuber were obtained with the ILs $[C_4C_1im][H_2PO_4]$ and $[C_4C_1im]Br$, respectively.⁵³ Du et al.⁵³ and Xu et al.⁵² also studied the ILs $[C_nC_1im]Br$, with $n = 2, 4$ and 6 , to infer on the effect of the cation alkyl chain length. The authors observed that the higher extraction yields were obtained with $[C_4C_1im]Br$, independently of the extracted flavonoid. Xu et al.⁵² investigated additional ILs, such as $[C_4C_1im][H_2PO_4]$, $[C_4C_1im][HSO_4]$ and $[(HOOC)C_1C_1im]Cl$, and concluded that

ILs such as $[C_4C_1im][HSO_4]$ and $[(HOOC)C_1C_1im]Cl$, which could provide enough H^+ to hydrolyse the flavonoids, display a strong hydrolysis ability and thus afford higher extraction yields. Finally, Du et al.⁵³ verified that pyridinium-based ILs provide higher extraction yields than their imidazolium-based counterparts. These overall results^{52,53} reveal that although the IL anion plays the major role, the IL cation effect cannot be discarded in the flavonoids extraction performance, as discussed before for the alkaloids. On the other hand, ILs composed of non-aromatic cations were not studied and no major conclusions on possible $\pi\cdots\pi$ and hydrogen-bonding interactions (between the target flavonoid and the IL cation) can be inferred at this stage. All authors⁵²⁻⁵⁴ selected $[C_4C_1im]Br$ as the best solvent for the extraction of flavonoids by IL-based MAE.

Xu et al.⁵² and Zeng et al.⁵⁴ demonstrated that the extraction yield of flavonoids is IL concentration-dependent (in aqueous solution). As discussed before with alkaloids, with flavonoids the extraction yield also increases up to a maximum with the IL concentration, and then stabilizes or starts decreasing for higher IL concentrations. Other extraction conditions were also optimized, namely the extraction time and the liquid-solid ratio.^{52,53} Both parameters increase significantly the extraction efficiency of flavonoids.^{52,53} However, the optimum extraction time and solvent volume for the flavonoids extraction are usually higher than those observed for alkaloids,^{48,49,52,53}

The particles' size and the temperature of extraction were also investigated.^{52,53} Both groups of researchers^{51, 52} observed that for particles smaller than 0.30-0.45 mm the extraction yield is almost constant or even decreases. When the particles are too small, the samples tend to agglomerate and the IL penetration into the natural matrix becomes more difficult.^{52,53} In addition, in both examples,^{52,53} it was observed a maximum in the flavonoids extraction at 60-80 °C. The increase of temperature decreases the viscosity of the IL solution, increasing thus the IL diffusion as well as the solubility of the flavonoids into the solvent as previously discussed. Nevertheless, at higher temperatures it was observed the degradation of flavonoids.⁵²⁻⁵⁴

Finally, the authors^{52,54} compared the IL-based MAE with more traditional extraction processes. Zeng et al.⁵⁴ showed that the IL-based MAE leads to a high rutin extraction yield (*Saururus chinensis* = 101.2 %; *Flos sophorae* = 99.6 %) with a lower solvent consumption and lower extraction time when compared to the optimized IL-based UAE (*Saururus chinensis* = 99.3 %; *Flos sophorae* = 98.2 %), IL-based heating extraction (*Saururus chinensis* = 98.6%; *Flos sophorae* = 99.7 %) and IL-based marinated extraction (*Saururus chinensis* = 97.5 %; *Flos sophorae* = 94.8 %). Xu et al.⁵² concluded that IL-based MAE is a more efficient technique for the extraction of kaempferol (\approx 0.05 mg/g), myricetin (\approx 0.04 mg/g) and quercetin (0.14 mg/g) from *Bauhinia championii* when compared to the conventional MAE and heating reflux extraction (kaempferol < 0.01 mg/g, myricetin < 0.01 mg/g and quercetin \approx 0.06 mg/g).

In 2011, Sun et al.⁵¹ described the application of IL-based UAE for the extraction of flavonoids from natural sources. The authors studied the use of ILs as alternative solvents in the extraction, separation and purification (by IL-based UAE followed by high-speed counter-current chromatography) of three isoflavones - tectoridin, iristectorin A and iristectorin B - from

Iris tectorum.⁵¹ The impact of different ILs, methanol and NaCl in the flavonoids extraction was firstly ascertained.⁵¹ The IL $[C_8C_1im]Br$ directed to the best results followed by $[C_6C_1im]Br$ and methanol.⁵¹ Further, the $[C_8C_1im]Br$ concentration on the extraction yield of flavonoids was investigated with a maximum on the extraction yield obtained at 0.5 M of IL (in aqueous solution). Sun et al.⁵¹ also verified that the increase on the time of extraction (up to 30 min) significantly improves the extraction yields. Longer times do not provide enhanced results due to a decrease on the diffusion rate. The solid-liquid ratio was finally addressed, and a maximum on the extraction yield at 30 mg/L was observed.⁵¹ After the optimization of all the operation conditions, Wang and co-workers⁵¹ finally proved that IL-based UAE extracts can be successfully separated and purified by high-speed counter-current chromatography as will be discussed latter in more detail.

75 Terpenoids

Terpenoids are the largest group of natural compounds present in biomass. These compounds are similar to terpenes, derived from isoprene units, and which may include some oxygen functionality or different rearrangements of the carbon skeleton. A large number of terpenoids present biological activities against cancer, inflammation, malaria, etc..¹⁰⁶

All the terpenoids extracted from natural sources by the application of ILs are described in Table 4. A total of 16 terpenoids, 39 ILs and 3 different separation processes were studied. As verified before with alkaloids and flavonoids, the most used ILs are 1-alkyl-3-methylimidazolium-based compounds with the anions Br^- , Cl^- and $[BF_4]^-$, in water or ethanol mixtures. Three works applying pure ILs were also reported.⁶⁰⁻⁶²

Within the application of IL-based MAE in the extraction of bioactive compounds from natural sources, Liu et al.⁵⁵ demonstrated that a terpenoid (carnosic acid), a phenolic acid (rosmarinic acid) and essential oils can be extracted from *Rosmarinus officinalis* (rosemary). The authors⁵⁵ studied a series of IL aqueous solutions in MAE and suggested a simultaneous extraction and distillation method. Amongst the several ILs investigated, the combination of Br^- and imidazolium with a long aliphatic moiety led to enhanced extraction yields.⁵⁵ These results are in agreement with those shown by Bica and co-workers⁴³ in the extraction of piperine. The extraction yield of carnosic acid increases significantly with the increase on the IL concentration (from 0.2 to 1 M of $[C_8C_1im]Br$ and well above the respective CMC). However, the extraction yield of rosmarinic acid increases until 0.6 M and a slight decrease is then observed for higher IL concentrations. Again, an increase on the solution viscosity seems to hinder an efficient extraction. Finally, and as investigated in other works, the solid-liquid ratio, the irradiation power and the extraction time were also optimized. An increase in the irradiation power and extraction time, and a decrease in the solid-liquid ratio, showed a positive effect on the extraction efficiencies of both the terpenoid and phenolic acid.⁵⁵ The authors compared the reported method with more conventional techniques and concluded that IL-based MAE requires a lower extraction time and provides higher extraction yields.⁵⁵

The application of IL-based UAE was also extended to the extraction of other terpenoids, such as ginsenoside-Rg1, -Re, -Rf,

Table 4 List of terpenoids extracted from natural sources using ILs or ILs solutions (the molecular solvent is presented between parentheses) and different extraction techniques employed.

Value-added compound	Natural source	Technique	IL
Carnosic acid	<i>Rosmarinus officinalis</i> (rosemary)	MAE	[C ₁₀ C ₁ im]Br, [C ₂ C ₁ im]Br, [C ₄ C ₁ im][BF ₄], [C ₄ C ₁ im][NO ₃], [C ₄ C ₁ im]Br, [C ₄ C ₁ im]Br, [C ₄ C ₁ im]Cl, [C ₆ C ₁ im]Br, [C ₈ C ₁ im]Br (water) ⁵⁵
Ginsenoside-Rg1, -Re, -Rf, -Rb1, -Rc, -Rb2, -Rb3, -Rd	Ginseng root		[C ₂ C ₁ im]Br, [C ₃ C ₁ im][BF ₄], [C ₃ C ₁ im]Br, [C ₃ C ₁ im]I, [C ₄ C ₁ im]Br, [C ₆ C ₁ im]Br (water) ⁵⁶
Cryptotanshinone			
Tanshinone I	<i>Salvia miltiorrhiza</i>	UAE	[C ₁₀ C ₁ im]Br, [C ₁₂ C ₁ im]Br, [C ₁₄ C ₁ im]Br, [C ₁₆ C ₁ im]Br, [C ₈ C ₁ im]Br, [C ₂ C ₁ im]Cl, [C ₄ C ₁ im]Cl, [C ₆ C ₁ im]Cl, [C ₈ C ₁ im]Cl (water) ^{57,58}
Tanshinone II A			
Astaxanthin	Shrimp waste		[C ₂ C ₁ im][BF ₄], [C ₄ C ₁ im][BF ₄], [C ₄ C ₁ im][C ₁ SO ₄], [C ₄ C ₁ im]Br, [C ₄ C ₁ im]Cl, [C ₆ C ₁ im][BF ₄], [(NH ₂) ₃ C ₃ C ₁ im]Br (ethanol) ⁵⁹
Artemisinin	<i>Artemisia annua</i>		[N _{11(2O)10}][C ₂ CO ₂], [N _{11(2OH)0}][C ₇ CO ₂] (pure IL) ⁶⁰
Limonene	Orange peels		[C ₄ C ₁ im]Cl, [aC ₁ im]Cl, [C ₂ C ₁ im][C ₁ CO ₂] (pure IL) ⁶¹
Betulin	Birch bark	SLE	[C ₂ C ₁ im][(C ₁) ₂ PO ₄], [C ₂ C ₁ im][BF ₄], [C ₂ C ₁ im][C ₂ CO ₂], [C ₂ C ₁ im][C ₃ CO ₂], [C ₂ C ₁ im][C ₃ CO ₂], [C ₂ C ₁ im][C ₁ CO ₂], [C ₂ C ₁ im][N(CN) ₂], [C ₂ C ₁ im][PF ₆], [C ₂ C ₁ im][Ntf ₂], [C ₂ C ₁ im]Br, [C ₂ C ₁ im]Cl, [C ₆ C ₁ im]Cl, [C ₆ C ₁ im]Cl, [C ₈ C ₁ im]Cl, [C ₁₀ C ₁ im]Cl, [C ₁₂ C ₁ im]Cl, [C ₁₄ C ₁ im]Cl, [aC ₁ im]Cl, [C ₁ C ₁ im][C ₃ CO ₂], [C ₁ C ₁ im][C ₁ CO ₂], [C ₄ C ₁ pyr]Cl, [C ₄ py]Cl, [(OH)C ₂ C ₁ im]Cl (pure IL) ⁶²

-Rb1, -Rc, -Rb2, -Rb3, -Rd, cryptotanshinone, tanshinone I, tanshinone II A and astaxanthin, from different natural sources.⁵⁶

⁵⁹ In all these works, 1-alkyl-3-methylimidazolium-based ILs were studied as extraction solvents (*cf.* Table 4). As usual⁵⁵, the authors investigated the effect of the IL chemical structure and some process variables.

¹⁰ Ginseng roots are commonly consumed by humans due to their anti-fatigue, cardio-protective, anti-diabetic and anti-tumour activities. Lin et al.⁵⁶ were the first to suggest the application of IL-based UAE for the extraction of ginsenosides. Amongst the several ILs investigated, [C₃C₁im]Br led to an extraction yield of ¹⁵ ≈ 15 mg/g. The IL concentration was also evaluated and a maximum on the extraction yield was observed at 0.3 M.⁵⁶ The solid-liquid ratio and the extraction time were additionally investigated and a solid-liquid ratio of 1:10 and an extraction time of 20 min were selected as the ideal conditions.⁵⁶ The extraction ²⁰ yields attained with [C₃C₁im]Br were also compared with those obtained with water or ethanol.⁵⁶ The results obtained clearly confirm the higher ability of the IL aqueous solution to extract ginsenosides (≈ 17 mg/g) when compared to water (≈ 13 mg/g) or ethanol (≈ 6 mg/g). Lastly, a comparison with the conventional ²⁵ UAE allowed to conclude that the proposed route provides higher extraction efficiencies (3.16 times increase) with shorter extraction times (reduction of 33% in time).⁵⁶

Wu et al.⁵⁸ and Bi et al.⁵⁷, in 2009 and 2011, respectively, published the application of IL-based UAE for the extraction of ³⁰ tanshinones from *Salvia miltiorrhiza*.¹⁰⁷ Similarly to the work carried out by Bica and co-workers⁴³ regarding the piperine extraction, Wu et al.⁵⁸ presented one of the most complete investigations on the use of long-alkyl chain ILs, [C_{*n*}C₁im]Br-based ILs (*n* = 8, 10, 12, 14, 16). The results attained suggest that ³⁵ the extraction of tanshinones is also micelle-mediated.⁵⁸ The best extractions were acquired with the IL with the longer alkyl chain ([C₁₆C₁im]Br) and the extraction yields were *ca.* 0.6, 1.2 and 1.4

mg/g for cryptotanshinone, tanshinone I and tanshinone II A, respectively.⁵⁸ The chemical structures of these terpenoids are ⁴⁰ presented in Fig. 9. The octanol-water partition coefficients of cryptotanshinone, tanshinone I and tanshinone II A are 5.6×10⁴, 2.9×10⁴ and 3.7×10⁵, respectively.⁹⁷ These terpenoids are very lipophilic molecules which support the results obtained. When dealing with aqueous solutions these type of compounds are ⁴⁵ better dissolved by a micelle-mediated process. On the other hand, the increase on the IL concentration in water, from 10 to 50 mM, has a significant effect on the extraction yields whereas above a concentration of 50 mM there is no effect.⁵⁸ The extraction time and the solid-liquid ratio were also investigated: ⁵⁰ 30 min of extraction time and a solid-liquid ratio of 1:80 showed to be enough to completely extract tanshinones.⁵⁸ The proposed method was successfully applied to the analysis of *Salvia miltiorrhiza* herbs from different sources.⁵⁸

Bi et al.⁵⁷ suggested the application of IL-based UAE for the ⁵⁵ extraction and pre-concentration of tanshinones, using chloride-based ILs, which can be further converted to their hydrophobic form by anion metathesis. Thus, in what concerns the IL chemical structure, only the cation alkyl side chain length was evaluated. Between [C₂C₁im]Cl and [C₆C₁im]Cl, the extracted amount of ⁶⁰ tanshinones increases slightly, whereas between [C₆C₁im]Cl and [C₈C₁im]Cl, it increases dramatically due the strong interactions occurring between the IL and the tanshinones.⁵⁷ The IL concentration of 0.50 M and a solid-liquid ratio of 1:40 were identified as the best conditions.⁵⁷ The ultrasonic power and a ⁶⁵ time of extraction above 105 W and 80 min, respectively, have no significant effect on the extracted amount of tanshinones.⁵⁷ The proposed technique was also compared with molecular solvent extractions, namely with water, ethanol, dichloromethane, ethyl acetate, etc.⁵⁷ The results obtained disclosed that the application ⁷⁰ of ILs improves the extracted amount of tanshinone I and tanshinone II A by at least three times.⁵⁷ After the extraction of

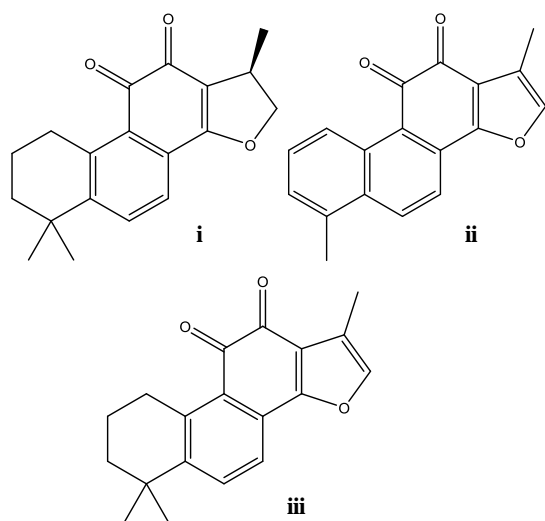


Fig. 9 Chemical structure of some terpenoids: (i) cryptotanshinone; (ii) tanshinone I; (iii) tanshinone II A.

5 tanshinones from *Salvia miltiorrhiza* herbs, the authors⁵⁷ proposed a novel pre-concentration process through the conversion of the IL into its hydrophobic form by anion metathesis. To this aim, HPF₆ and LiNTf₂ were added in order to convert the [C₈C₁im]Cl into the hydrophobic ILs [C₈C₁im][PF₆]
 10 and [C₈C₁im][NTf₂].⁵⁷ [C₈C₁im][PF₆] was selected as the best option since it showed a higher affinity for tanshinones. With this pre-concentration route, the tanshinone I, tanshinone II A and cryptotanshinone enrichment factors were 25.4, 29.1 and 28.5, respectively.⁵⁷
 15 Bi et al.⁵⁷ not only reported the application of IL-based UAE for the tanshinones extraction from *Salvia miltiorrhiza*, but also studied the application of this technique for the extraction of astaxanthin from shrimp waste (a non-vegetable source).⁵⁹ Shrimp waste represents ca. 65 % of the initial shrimp weight and
 20 its processing leads to severe environmental concerns.¹⁰⁸ However, many bioactive compounds can be recovered from these residues, such as astaxanthin.¹⁰⁹ This is the most valuable carotenoid with a price of ≈ \$US320 per mg.⁵⁹ Bi et al.⁵⁹ started their work with the selection of the molecular solvent, namely
 25 water, methanol, ethanol, *n*-hexane, ethylacetate, acetone and dichloromethane. Ethanol conferred the best results to the astaxanthin extraction from shrimp waste.⁵⁹ Then, the IL effect in ethanol solutions was investigated with bromide-based ILs.⁵⁹ It should be remarked that this work uses alcoholic solutions of ILs
 30 and not aqueous solutions as commonly reported in literature based on a previous choice of the optimum molecular solvent.⁵⁹ The finest results were obtained with the functionalized [(NH₂)C₃C₁im]Br, ca. 80 μg of astaxanthin per g of dried shrimp waste, due to the existence of a reductive amine group. This
 35 group protects astaxanthin against oxidation and has favourable interactions with the carotenoid functional groups. The effect of the [(NH₂)C₃C₁im]Br concentration in ethanol was also analysed with the astaxanthin extraction increasing up to 0.50 M of IL.⁵⁹ A significant increase on the extraction efficiency was observed up to 60 min; after that no further improvement was observed.⁵⁹ The
 40 solid-liquid ratio of 1:10 was selected taking into account

economic considerations.⁵⁹

Artemisinin is a sesquiterpene lactone with pivotal importance in the malaria treatment due its very fast action against the
 45 widespread *Plasmodium falciparum*.¹¹⁰ This value-added compound is typically extracted from *Artemisia annua* using petroleum ether, heptane, hexane or toluene at high temperatures.¹¹¹ However, in 2006, Bioniqs Ltd. (UK)¹¹² initiated a preliminary study on the possibility of using ILs as solvents in
 50 the SLE of artemisinin from *Artemisia annua*. Amongst the several ILs investigated, the biodegradable IL [N_{11(2OH)0}][C₇CO₂] was identified as the best extraction solvent while presenting comparable results to those obtained by hexane at high temperatures.¹¹¹ However, in 2006, Bioniqs Ltd. (UK)¹¹² initiated a preliminary study on the possibility of using ILs as solvents in
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 60 determined: a solid-liquid ratio of 1.1 at 25 °C for 30 min.¹¹² Later on, in 2008, Bioniqs went further in this study and designed an IL with an even better performance.⁶⁰ Molecular simulation studies were carried out to gather a deeper insight into the interactions between the IL, artemisinin and water (in a 3-
 65 component system). This study led to the modification of the IL from [N_{11(2OH)0}][C₇CO₂] to [N_{11(2(O)1)0}][C₂CO₂] with a significant improvement on the selective extraction of artemisinin.⁶⁰ Nevertheless, at this stage, Bioniqs Ltd. considers that [N_{11(2(O)1)0}][C₂CO₂] is not a final and optimized product ready for
 an in-field deployment, but only represents a step further on the long path of refining and developing an optimized IL.⁶⁰

The study on the potential of artemisinin against malaria is a top priority issue and, in the end of 2009, it was published a Chinese patent regarding the use of an IL-based UAE process for
 70 the extraction of this biomolecule from *Artemisia annua*.¹¹³ To the best of our knowledge this is the first patent regarding the application of ILs in the extraction of value-added compounds from biomass.

In 2011, Bica and co-workers⁶¹ suggested the application of
 75 pure ILs for the dissolution of orange essential oils, such as limonene. Limonene is a cyclic monoterpene and is commonly used in cosmetics and as a flavouring chemical. Due to the antimicrobial properties it is becoming very popular as a biodegradable insecticide and an alternative cleanser.⁶¹ Initially,
 80 the ability of several ILs ([C₄C₁im]Cl, [aC₁im]Cl and [C₂C₁im][C₁CO₂]) for the complete dissolution of orange peels was investigated. The complete dissolution of orange peels was observed after 3 h with [C₂C₁im][C₁CO₂], while even after 24 h the ILs [C₄C₁im]Cl and [aC₁im]Cl provided only a partial
 85 dissolution.⁶¹ The liquid solutions were then subjected to vacuum distillation at 60–65 °C and a distilled fraction composed of two layers, limonene and water, was finally obtained allowing the isolation of limonene.⁶¹ The use of pure [C₂C₁im][C₁CO₂] loaded with orange peel at 35 wt % led to a yield on the isolated
 90 orange oil of 4.9 %.⁶¹ Moreover, by GC-MS and NMR spectroscopy it was concluded that limonene was obtained in a high purity level and that no traces of IL degradation products were observed.⁶¹

One year later, the same research group suggested the use of
 95 IL-based SLE to extract the pharmaceutically active triterpene betulin from birch bark.⁶² This compound presents a versatile pharmaceutical potential due to its antitumor, antiviral and antimalarian properties. Furthermore, some of the betulin derivatives (for example, betulinic acid and bevirimat) are

potential contributors into the development of a new anti-HIV drug that it is already in clinical trials.^{114,115}

Nowadays, the betulin extraction is performed with high temperature boiling hydrocarbons, chlorinated solvents or with water-alcohol azeotropic mixtures. Besides the lengthen extractions of limited yields, a very low selectivity is also achieved which requires the further use of chromatographic steps to obtain betulin at a pharmaceutical-level purity.⁶² Aiming at improving the extraction yield and final purity of betulin extracted from birch bark, Ressmann et al.⁶² initially carried a study on the selection of pure ILs regarding their potential for biomass dissolution. Then, the authors⁶² analysed the performance of such ILs for the selective extraction of betulin and reached the following conclusions: (i) the increase of the alkyl chain length of $[C_nC_1im]Cl$ -based ILs until $[C_8C_1im]Cl$ affects slightly the isolation yield with $[C_4C_1im]Cl$ presenting the best result of ~32 wt %; when the longest alkyl chain at the imidazolium cation is longer than octyl the IL dissolution ability drastically decreases; (ii) the introduction of functional groups in the cation core ($[aC_1im]Cl$ and $[(OH)C_2C_1im]Cl$) lead to comparable results with those obtained with shorter alkyl chain $[C_nC_1im]Cl$ ILs; (iii) the results attained with $[C_4pyr]Cl$ and $[C_4C_1pyr]Cl$ are similar to those obtained with $[C_4C_1im]Cl$; (iv) $[C_2C_1im]Cl$, $[C_2C_1im]Br$, $[C_2C_1im][N(CN)_2]$, $[C_2C_1im][(C_1)_2PO_4]$ and $[C_2C_1im][C_1CO_2]$ lead to the best betulin yields (28 to 31 wt %) when compared to more hydrophobic ILs composed of anions such as $[BF_4]^-$, $[PF_6]^-$ and $[Ntf_2]^-$ (~22 wt %)¹¹⁶ (v) with the exception of $[C_1C_1im][C_1CO_2]$, all the other studied carboxylate-based ILs (cf. Table 4) revealed a good dissolution capacity and a high betulin yield between 30-31 wt %.⁶² Overall, $[C_2C_1im][C_1CO_2]$ was selected as the best solvent for dissolving birch bark and was used in subsequent betulin extraction experiments. After, a solid-liquid ratio of 10 wt % was selected

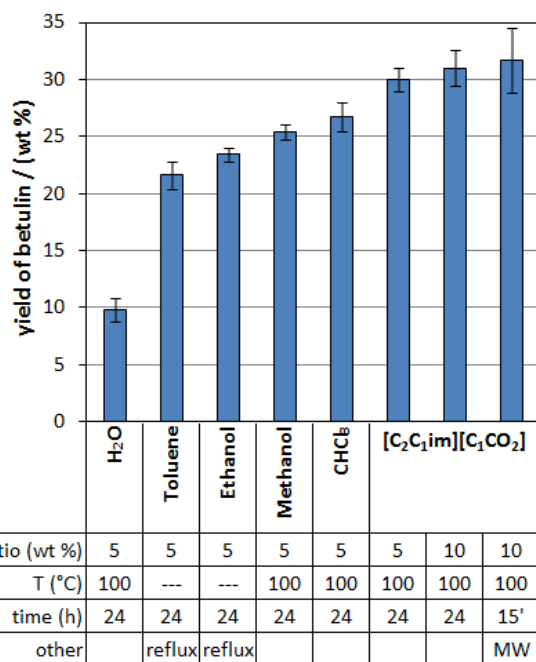


Fig. 10 Influence of the extraction solvents and operational conditions on the isolation of betulin from birch bark.⁶²

and the application of microwave-based extraction with heating at 100 °C showed to significantly reduce the extraction time from 24 h to 15 min. Analyzing Fig. 10 it is possible to conclude that the IL-based extraction process suggested by Ressmann et al.⁶² is a potential route for the extraction of betulin when compared with the application of conventional volatile organic solvents.

Benzofuranoids, benzopyranoids, lignans and phenolic acids

Besides the three major classes of high-value compounds discussed above, other natural products were also investigated albeit in a reduced extent. The extraction of benzofuranoids, benzopyranoids, lignans and phenolic acids from natural sources using IL-based media is discussed here as a whole group. All the extracted natural compounds, and the methods and ILs studied in their extraction, are listed in Table 5. MAE and UAE were the most studied extraction techniques applying water-IL mixtures.^{50,53,55,63-66} ILs composed of 1-alkyl-3-methylimidazolium cations combined with the anions Br^- , Cl^- and $[BF_4]^-$ were, again, the most investigated.

Senkyunolide H, senkyunolide I and Z-ligustilide are benzofuranoids existent in the traditional Chinese medicine herb *Ligusticum chuanxiong*. In order to find a more benign and efficient extraction process, Yansheng et al.⁶³ suggested the application of IL-based MAE for the extraction of these bioactive compounds. In addition, the authors⁶³ used a new class of low toxicity protic ILs composed of an ammonium-based cation and the propionate anion ($[N_{11(2(O)2OH)0}][C_2CO_2]$ and $[N_{11(3N)0}][C_2CO_2]$). This is the third work reported where the extraction of value-added chemicals was carried out by means of protic ILs.^{50,63} Besides the influence of the IL chemical structure, the temperature, extraction time, solid-liquid ratio and particle size effects were also evaluated.⁶³ The IL impact on the extraction of benzofuranoids showed to be highly dependent on other operational parameters as well as on the biomolecule itself. However, in general, $[N_{11(3N)0}][C_2CO_2]$ leads to higher extraction yields.⁶³ While the extractions of senkyunolide H and Z-ligustilide are not very dependent on temperature (between 60 and 180 °C), the extraction of senkyunolide I increases significantly with temperature.⁶³ For both the ILs investigated the extraction of the three benzofuranoids was found to be complete after 1 min, with the exception of senkyunolide I extracted with $[N_{11(3N)0}][C_2CO_2]$ (5 min required). Finally, the biomass particles size and the solid-liquid ratio showed to have no significant effect on the extraction.⁶³

Yang et al.⁶⁴ proposed the application of IL-based UAE for the extraction of two benzopyranoids from *Fraxinus rhynchophylla*: aesculetin and aesculin. As in other works contemplating IL-based UAE processes, the effects of the IL anion and cation were extensively investigated with a wide variety of ILs: $[C_7H_7C_1im]Br$, $[C_7H_7C_1im]Cl$, $[C_{10}C_1im]Br$, $[C_{12}C_1im]Br$, $[C_2C_1im][BF_4]$, $[C_2C_1im]Br$, $[C_4C_1im][BF_4]$, $[C_4C_1im][ClO_4]$, $[C_4C_1im][HSO_4]$, $[C_4C_1im][Tos]$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$, $[C_4C_1im]I$, $[C_8C_1im]Br$, $[C_6C_1im]Br$, $[(HSO_3)C_4C_1im][HSO_4]$ and $[(OH)C_2C_1im]Cl$.⁶⁴ Generally, the extraction efficiencies attained range between 60 and 100 %.⁶⁴ Taking into account the hard-task on the synthesis of some ILs, the authors concluded that bromide-based ILs are the most appropriate.⁶⁴ Regarding the cation alkyl side chain length in 1-alkyl-3-methylimidazolium-based ILs, $[C_4C_1im]$ -based fluids

lead to the best extractive performance with extraction yields up to ca.100 %. In summary, [C₄C₁im]Br was selected as the best candidate for application in IL-based UAE, and other extraction factors were additionally adjusted.⁶⁴ As previously discussed, for other value-added compounds and other ILs, there is a maximum on the extraction yields as a function of the IL concentration.⁶⁴ The extraction efficiency increases with the ultrasonic power and 100 % of extraction was achieved at 250 W. Furthermore, the ultrasonic time had a great impact on the extraction efficiencies. Up to a solid-liquid ratio of 10 mg/L the extraction efficiency increases significantly whereas for higher values it becomes almost constant.⁶⁴ As a final point, the authors compared the proposed methodology with conventional UAE using several molecular solvents, and with the ethanol-based heating reflux extraction and a simple stirring extraction. The overall comparison on the extraction yields between the three methods is depicted in Fig. 11. Based on this comparison, IL-based UAE is the most efficient technique since it leads to higher extraction yields while reducing the extraction time, and is thus a more economical and environmentally-friendly route for the extraction of benzopyranoids.⁶⁴

In 2011, Ma et al.^{65,66} reported the application of IL-based UAE and MAE for the extraction of four lignans from the fruits of *Schisandra chinensis* – schizandrin, schisantherin A,

25 deoxyschizandrin and γ -schizandrin. All these lignans display anti-hepatotoxic, antioxidant and anti-inflammatory characteristics.

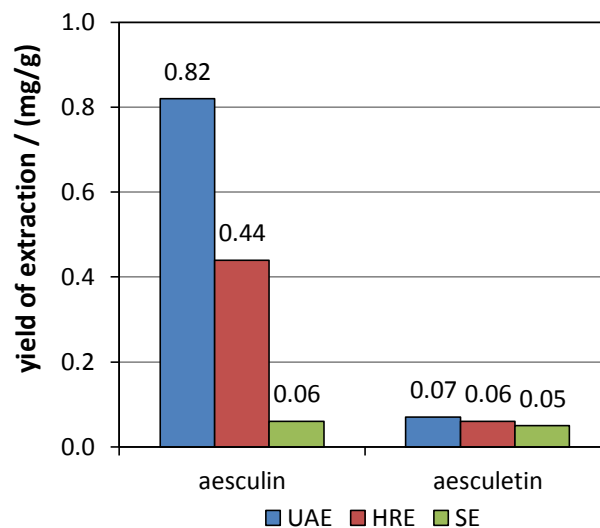


Fig. 11 Yield of extraction of aesculin and aesculetin by three extraction methods/solvents.⁶⁴ HRE – heating reflux extraction; SE – stirring extraction.

Table 5 List of different families extracted from natural sources using ILs or ILs solutions (the molecular solvent is presented between parentheses) and different extraction techniques employed.

Value-added compound	Natural source	Technique	IL
Benzofuranoids			
Senkyunolide H	<i>Ligusticum chuanxiong</i>	MAE	[N _{11(2(O)2OH)0}][C ₂ CO ₂], [N _{11(3N)0}][C ₂ CO ₂] (pure IL) ⁶³
Senkyunolide I			
Z-Ligustilide			
Benzopyranoids			
Aesculetin	<i>Fraxinus rhynchophylla</i>	UAE	[C ₇ H ₇ C ₁ im]Br, [C ₇ H ₇ C ₁ im]Cl, [C ₁₀ C ₁ im]Br, [C ₁₂ C ₁ im]Br, [C ₂ C ₁ im][BF ₄], [C ₂ C ₁ im]Br, [C ₄ C ₁ im][BF ₄], [C ₄ C ₁ im][ClO ₄], [C ₄ C ₁ im][HSO ₄], [C ₄ C ₁ im][Tos], [C ₄ C ₁ im]Br, [C ₄ C ₁ im]Cl, [C ₄ C ₁ im]I, [C ₈ C ₁ im]Br, [C ₆ C ₁ im]Br, [(HSO ₃)C ₄ C ₁ im][HSO ₄], [(OH)C ₂ C ₁ im]Cl (water) ⁶⁴
Aesculin			
Lignans			
Deoxyschizandrin	<i>Schisandra chinensis</i>	UAE and MAE	[C ₁₀ C ₁ im]Br, [C ₁₂ C ₁ im]Br, [C ₂ C ₁ im]Br, [C ₄ C ₁ im][BF ₄], [C ₄ C ₁ im][C ₂ CO ₂], [C ₄ C ₁ im][ClO ₄], [C ₄ C ₁ im][HSO ₄], [C ₄ C ₁ im][NO ₃], [C ₄ C ₁ im][OH], [C ₄ C ₁ im]Br, [C ₆ C ₁ im]Br, [C ₈ C ₁ im]Br (water) ^{65,66}
Schisantherin A			
Schizandrin			
γ -Schizandrin			
Phenolic acids			
Ellagic acid	<i>Acacia catechu</i> (catechu) and <i>Terminalia chebula</i> (myrobolan)	SLE	[N ₁₁₀₀][N(C ₁) ₂ CO ₂] (pure IL) ⁵⁰
Gallic acid	<i>Psidium guajava</i> and <i>Smilax china</i>	MAE	[C ₂ C ₁ im][BF ₄], [C ₂ C ₁ im]Br, [C ₄ C ₁ im][BF ₄], [C ₄ C ₁ im][C ₁ SO ₄], [C ₄ C ₁ im][H ₂ PO ₄], [C ₄ C ₁ im][N(CN) ₂], [C ₄ C ₁ im]Br, [C ₄ C ₁ im]Cl, [C ₄ py]Cl, [C ₆ C ₁ im]Br (water) ⁵³
Rosmarinic acid			<i>Rosmarinus officinalis</i> (rosemary)

The authors^{65,66} studied aqueous solutions of a large number of ILs (cf. Table 5) and some extraction conditions of MAE and UAE were also optimized. Amongst the studied [C₄C₁im]-based ILs, the [C₄C₁im]Br led to the better results in IL-based UAE with 100% of extraction of all lignans.⁶⁶ The authors also investigated the cation alkyl chain length ([C_nC₁im]⁺ with $n = 2-12$) and [C₁₂C₁im]Br showed to be the best solvent.⁶⁶ Also for lignans, it seems that surface-active ILs perform better and that they are extracted by a micelle-mediated extraction process. In general, an increase in the ultrasonic power increases the extraction efficiency.⁶⁶ The ultrasonic time has a significant effect until ca. 30 min, and after which the extraction efficiency remains almost constant.⁶⁶ In summary, and weighing the equilibrium between the extraction efficiency and time, and solvent and energy consumption, the authors concluded that three individual extractions lead to extraction yields of 95 % and are the best choice.⁶⁶ The IL-based UAE method was finally compared with conventional heating reflux extraction techniques and it was concluded that the proposed approach provides higher extraction efficiencies (~ 3.5 fold) in shorter times (reduction from 6 h to 30 min).⁶⁶

As verified with UAE, also in MAE, the combination of the bromide-based and [C₁₂C₁im]-based ILs led to the best extraction efficiencies with a total yield of lignans of ≈ 99 and > 200 mg/kg, respectively.⁶⁵ Thus, the IL [C₁₂C₁im]Br was selected for the optimization of other parameters.⁶⁵ The authors verified that 40 min of microwave irradiation was the optimum time, at which the extraction of essential oils and lignans from *Schisandra chinensis* was complete.⁶⁵ The extraction yields also depend on the IL concentration in aqueous media with an increase on the extraction yield up to 0.25 M.⁶⁵ Moreover, an irradiation power of 385 W was adopted since higher values result in a drastic temperature increase and on the carbonization of the raw materials, and isomerisation or thermal instability of lignans.⁶⁵ The decrease on the solid-liquid ratio until 1:12 significantly increases the extraction yield.⁶⁵ Finally, and comparing with conventional hydro-distillation, steam-distillation and reflux extraction methods, the IL-MAE approach allows to simultaneously obtain essential oils and lignans along with a lower energy and time consumption.⁶⁵

Ma et al.^{65,66} did not make any comparison between the two published works; yet, the compilation of their results on the lignans extraction allowed us to verify that similar extraction conditions lead to the best performances in UAE and MAE. The main differences between UAE and MAE appear in the heat and mass diffusion coefficients: UAE increases the mass transfer while MAE allows a fast heat transfer into the solvent solution. Depending on the target compounds, both methods could present similar or distinct performances. Nevertheless, and in general, when dealing with thermally sensitive value-added compounds, the UAE is certainly the best option since it can be performed at room temperature. On the other hand, when considerable viscous solutions are used, such as pure or highly concentrated solutions of ILs, MAE allows the decrease of the viscosity by heating, thus increasing the mass transfer. Besides these two more energy-consumption approaches, the best process is always a simple SLE carried out at room temperature and using water as the main solvent. However, a prior critical analysis of the time required for

a complete extraction, and thus an accurate evaluation of the energy consumption, should be carried out. Before any extraction, the target high-value compound, the biomass structure and its composition should be also evaluated and a real screening on the best extraction method and solvent should be beforehand considered.

Ellagic, gallic and rosmarinic acids are examples of phenolic acids which are commonly extracted together with other compounds from biomass. Du et al.⁵³ reported the extraction of both ellagic and gallic acid, along with quercetin and trans-resveratrol, from *Psidium guajava* and *Smilax china* by IL-based MAE. Chowdhury et al.⁵⁰ suggested the application of SLE for the extraction of ellagic and gallic acids, pyrocatechol and catechin from *Acacia catechu* and *Terminalia chebula*. Liu et al.⁵⁵ reported the extraction of rosmarinic acid, together with carnolic acid and essential oils from rosemary by IL-based MAE. All these works^{50,53,55} were described above.

Simple and polycyclic aromatic compounds

The simple and polycyclic aromatic compounds addressed in this section include polyketide or shikimate related compounds. The chemical structure of some simple and polycyclic aromatic compounds is shown in Fig. 12. All the simple and polycyclic aromatic compounds extracted from natural sources, using pure ILs or ILs solutions as extraction solvents, are described in Table 7. Ethanol and water were used as molecular solvents, three separation techniques were applied, namely SLE, MAE and UAE, as well as 10 ILs, mainly [C_nC₁im]-based fluids.

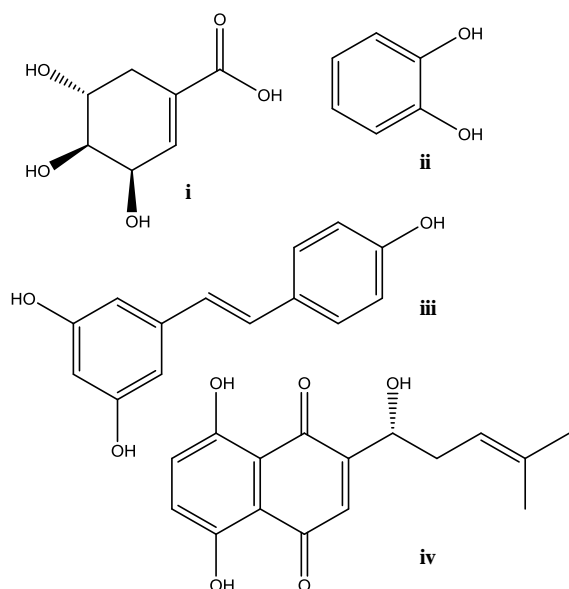
Pyrocatechol is a simple aromatic compound which was already extracted from *Acacia catechu* and *Terminalia chebula* using a distillable IL.⁵⁰ Also, the polycyclic aromatic compound trans-resveratrol was extracted from *Psidium guajava* and *Smilax china* by an IL-based MAE.⁵³ These processes were described in detail in previous sections regarding the extraction of (+)-catechin and quercetin.^{48,53}

In 2007, Li and co-workers³⁹ reported the extraction of trans-resveratrol from an additional natural source (*Rhizma polygoni*) by IL-based MAE.³⁹ The authors investigated the effect of the IL chemical structure ([C₄C₁im][BF₄], [C₄C₁im]Br and [C₄C₁im]Cl) in addition to the operational conditions which were optimized by an orthogonal design L₉ (3⁴) approach.³⁹ The best results were obtained with [C₄C₁im]Br in contrast with [C₄C₁im][BF₄] which was shown to be the less effective IL. It was also verified that the extraction yield increases with the IL concentration.³⁹ From the orthogonal design results, the following optimized conditions were found: 0.30-0.45 mm of particles size, solid-liquid ratio of 1:20, extraction temperature of 60 °C and extraction time of 10 min.³⁹ It should be remarked that these parameters are very similar to the conditions found in the extraction of alkaloids and flavonoids previously discussed.^{48,49,52-54} A 93% of trans-resveratrol extraction yield was attained at the optimum conditions.³⁹

Shikimic acid is the starting material for the production of the neuraminidase inhibitor TamifluTM (oseltamivir phosphate) which is used in the treatment and prevention of influenza.^{117,118} In the conventional manufacturing process, shikimic acid is converted into shikimic acid ethyl ester followed by an acetonide or diethyl ketal intermediate that is subsequently transformed into the final

Table 7 List of aromatic compounds extracted from natural sources using ILs or ILs solutions (the molecular solvent is presented between parentheses) and different extraction techniques employed.

Value-added compound	Natural source	Technique	IL
Shikimic acid	<i>Illicium verum</i> (star anise)	MAE	[C ₂ C ₁ im][BF ₄], [C ₂ C ₁ im][CF ₃ SO ₃], [C ₂ C ₁ im][C ₁ CO ₂], [C ₂ C ₁ im][Ntf ₂], [C ₂ C ₁ im][PF ₆], [C ₂ C ₁ im]Cl (pure IL) ⁶⁷
	<i>Ginkgo biloba</i>	SLE	[C ₂ im][HSO ₄], [C ₂ C ₁ im][HSO ₄], [(HSO ₃)C ₄ C ₁ im][H ₂ PO ₄], [(HSO ₃)C ₄ C ₁ im][HSO ₄], [(HSO ₃)C ₄ C ₁ im][Ntf ₂], [(HSO ₃)C ₄ C ₁ im]Br, [(HSO ₃)C ₄ C ₁ im]Cl (ethanol) ⁶⁸
Pyrocatechol	<i>Acacia catechu</i> (catechu) and <i>Terminalia chebula</i> (myrobolan)		[C ₄ C ₁ im]Cl (pure IL) ⁶⁹
	<i>Psidium guajava</i> and <i>Smilax china</i>	MAE	[C ₂ C ₁ im][BF ₄], [C ₂ C ₁ im]Br, [C ₄ C ₁ im][BF ₄], [C ₄ C ₁ im][C ₁ SO ₄], [C ₄ C ₁ im][H ₂ PO ₄], [C ₄ C ₁ im][N(CN) ₂], [C ₄ C ₁ im]Br, [C ₄ C ₁ im]Cl, [C ₄ py]Cl, [C ₆ C ₁ im]Br (water) ⁵³
Trans-resveratrol	<i>Rhizma polygoni</i>		[C ₄ C ₁ im][BF ₄], [C ₄ C ₁ im]Br, [C ₄ C ₁ im]Cl (water) ³⁹
Shikonin β,β'-dimethylacrylshikonin	<i>Arnebia euchroma</i>	UAE	[C ₂ C ₁ im][BF ₄], [C ₄ C ₁ im][BF ₄], [C ₆ C ₁ im][BF ₄], [C ₆ C ₁ im][PF ₆], [C ₈ C ₁ im][BF ₄], [C ₈ C ₁ im][PF ₆] (pure IL) ⁷⁰

**Fig. 12** Chemical structure of aromatic natural compounds: (i) shikimic acid; (ii) pyrocatechol; (iii) trans-resveratrol; (iv) shikonin.

drug. Shikimic acid is mostly extracted from the Chinese herb *Illicium verum* (star anise) with an isolation yield of 3-7 %, and responsible for the world-wide shortage in Tamiflu observed in 2005.^{119,120}

Motivated by the urgent requirement on finding alternative and effective techniques for the extraction of shikimic acid, Ressmann et al.⁶⁸ reported the dissolution of *Illicium verum* in the presence of Brønsted acidic IL solutions, both as solvents and catalysts, envisaging the synthesis of shikimic acid ethyl ester and the ketal ester (*in situ*). The authors⁶⁸ investigated the conversion of shikimic acid into ethyl ester in ethanol solutions of [(HSO₃)C₄C₁im][HSO₄], [(HSO₃)C₄C₁im][Ntf₂], [(HSO₃)C₄C₁im]Br and [(HSO₃)C₄C₁im]Cl. High conversions into ethyl ester (81 to 99 %) were observed, albeit the complete conversion was only attained with [(HSO₃)C₄C₁im][Ntf₂]. After

several experiments, the authors concluded that the sulfonic acid group in the side chain of the cation is responsible for the catalytic activity in the reaction.⁶⁸ After this first attempt, the reactive dissolution of star anise seeds was then studied in [(HSO₃)C₄C₁im][HSO₄] + ethanol solutions.⁶⁸ An extraction yield of 12.7 % was obtained when a mass-equivalent amount of [(HSO₃)C₄C₁im][HSO₄] was used.⁶⁸ Additional parameters were also evaluated. As observed in most works, the increase of the IL concentration leads to an increase on the extraction yield.⁶⁸ The application of microwave irradiation drastically reduces the reaction time (from 24 h to 30 min).⁶⁸ Based on these results, Ressmann et al.⁶⁸ developed an *in situ* process for the conversion of shikimic acid that uses a mixture of ethanol + 3-pentanone catalysed by [(HSO₃)C₄C₁im][HSO₄] or [(HSO₃)C₄C₁im][Ntf₂]. Although the process reported does not allow the recovery of the IL, it completely eliminates the use of the toxic and corrosive thionyl chloride commonly employed, while reducing the number of operational steps with improved yield.

Two years later, the same research group expanded their studies toward a better understanding on the IL-solute interactions.⁶⁷ Bica and co-workers⁶⁷ focused on [C₂C₁im]-based ILs that presented different abilities for the cellulose processing and biomass dissolution (*cf.* Table 7). [C₂C₁im][C₁CO₂] was used for the operational conditions optimization: (i) a low solid-liquid ratio (1 wt %) was required for a good dissolution of biomass in the IL; and (ii) the microwave irradiation shows, as before, that it can be advantageous in biomass processing by drastically reducing the time required to extract shikimic acid (from 24 h to 10 min at 100 °C).⁶⁷ [C₂C₁im][C₁CO₂] led to the best results (10.7 wt %) followed by other hydrophilic ILs, namely [C₂C₁im][CF₃SO₃] (10.3 wt %) and [C₂C₁im]Cl (10.0 wt %). On the other hand, the hydrophobic ILs presented the poorest results and in the case of [C₂C₁im][PF₆] the authors believe that shikimic acid suffers some degradation.⁶⁷ This degradation can be a major consequence of the hydrolysis of the hexafluorophosphate anion at high temperatures (100°C) and further production of hydrofluoric acid.⁸⁴

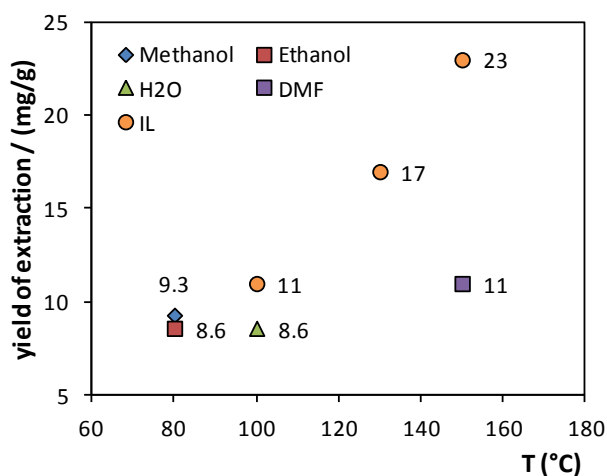


Fig. 13 Yield of shikimic acid extraction from *Ginkgo biloba* using different extraction methods at distinct temperatures.⁶⁹

Transmission electron microscopy (TEM) was also applied to infer on the biomass morphology after dissolution in the IL.⁶⁷ [C₂C₁im][C₁CO₂] almost completely dissolved the star anise and destroyed its original structure, while [C₂C₁im][PF₆] does not change the biomass morphology.⁶⁷ These changes in the biomass morphology are in close agreement with those observed before by other authors.⁴²

Since the quantities of shikimic acid still remain restricted to the amounts of available star anise it is vital to find alternative resources. Usuki et al.⁶⁹ suggested the extraction and isolation of this biomolecule from *Ginkgo biloba* leaves, a “living fossil” that is cultivated worldwide. Pure [C₄C₁im]Cl was selected as the extraction solvent and the obtained results, at different temperatures (100, 130 and 150 °C), where compared with methanol (80 °C), ethanol (80 °C), deionized water (100 °C) and dimethylformamide (DMF) (150 °C) mediated extractions.⁶⁹ From Fig. 13 it is possible to conclude that the extraction yield of shikimic acid increases with temperature. At 150 °C, the extraction yield was 2.5 times higher than that obtained with methanol at 80 °C and 2 times higher than with DMF at the same temperature. Thus, even pure ILs seem to be a good alternative to the conventional solvents commonly employed in the extraction of shikimic acid.⁶⁹ Nevertheless, from a greener and low-cost perspective, aqueous solutions should be always investigated.

Shikonin and β,β'-dimethylacrylshikonin are two bioactive compounds present in *Arnebia euchroma*, with anti-inflammatory, antibacterial, antitumor and antiviral characteristics.¹²¹ Xiao et al.⁷⁰ reported the application of IL-based UAE, using pure ILs, for the extraction of these compounds. As usual, the IL chemical structure effect was firstly evaluated.⁷⁰ The application of [C_nC₁im][BF₄] ILs revealed that as *n* increases, the extraction yield of β,β'-dimethylacrylshikonin significantly increases, whereas the extraction yield of shikonin only increases slightly.⁷⁰ From their molecular structure, it is evident that β,β'-dimethylacrylshikonin presents a more hydrophobic character than shikonin, and thus hydrophobic ILs are better extraction solvents for this compound. In addition,

higher extraction yields were observed with smaller particles. Compared to conventional UAE and soxhlet extraction, the IL-based UAE showed similar performance (0.35 and 2.21 μg/mg for shikonin and β,β'-dimethylacrylshikonin, respectively) with a significantly lower amount of sample, and lower time and solvent consumption.⁷⁰

Mixtures of value-added compounds

In nature it is possible to find several mixtures of value-added compounds with relevant pharmacological interest. Some of them are well-known, such as essential oils mixtures and the natural wax suberin. In this section, the published works dealing with the extraction of these mixtures from bioresources, using IL-based processes, will be discussed. All the mixtures of natural compounds extracted from biomass by pure ILs or ILs solutions as solvents are listed in Table 8.

Zhai et al.⁷³ reported, for the first time in 2009, the application of IL-based MAE for the extraction of essential oils from *Illicium verum* and *Cuminum cyminum*. Two years later, in 2011, Ma et al.⁶⁵ also studied the application of IL-based MAE for the extraction of essential oils and lignans from *Schisandra chinensis*. Later on, Liu et al.⁵⁵ and Jiao et al.^{71,72} reported the same technique for the extraction of essential oils from *Rosmarinus officinalis* (rosemary), *Dryopteris fragrans* and *Fructus forsythia*. The works of Ma et al.⁶⁵ and Liu et al.⁵⁵ were described in a previous section since essential oils were concomitantly extracted with the lignans deoxyschizandrin, schisantherin A, schizandrin and γ-schizandrin, and with the carnosinic and rosmarinic acids.

Zhai et al.⁷³ employed pure [C₆C₁im][PF₆] for the extraction of essential oils and optimized further experimental parameters, namely the solid-liquid ratio and the microwave power (1.5:20 and 440 W). Then, GC-MS was applied to the extracts to confirm the presence of essential oils.⁷³ The authors showed that there are no major differences between the constituents of the essential oils obtained by IL-based MAE when compared with the hydrodistillation technique.⁷³ However, the IL-based MAE makes the extraction process simpler and faster (from 180 to 15 min).⁷³

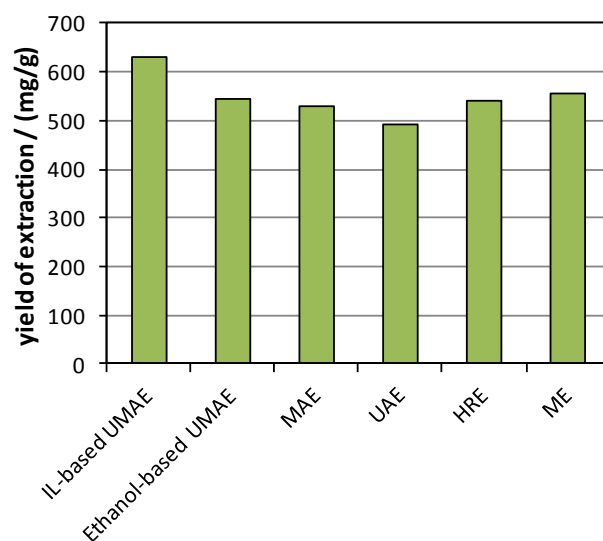
Jiao et al.^{71,72} studied the application of several ILs – [aC₁im]Cl, [C₂C₁im][C₁CO₂], [C₄C₁im]Br and [C₄C₁im]Cl – as extractive solvents coupled to MAE, followed by a hydrodistillation for the recovery of essential oils from *Dryopteris fragrans* and *Fructus forsythiae*.^{71,72} The results obtained reveal that [C₂C₁im][C₁CO₂] is the best candidate.^{71,72} Other operational parameters were optimized by central composite design and a first order kinetic model.^{71,72} At the optimum conditions (irradiation power of 300 W, pre-treatment temperature of 76 °C, [C₂C₁im][C₁CO₂] at 67 wt% and a pre-treatment time of 2.2 min for *Dryopteris fragrans* and irradiation power of 300 W, pre-treatment temperature of 86 °C, [C₂C₁im][C₁CO₂] at 77 wt % and pre-treatment time of 4.3 min for *Fructus forsythiae*) a significant increase on the yield of essential oils was observed.^{71,72} GC-MS analyses also confirmed that there were no considerable modifications in the chemical composition of these oils.^{71,72}

Table 8 List of mixtures of added-value compounds extracted from natural sources using ILs or ILs solutions (the molecular solvent is presented between parentheses) and different extraction techniques employed.

Value-added compound	Natural extract	Method	IL
Essential oils	<i>Dryopteris fragrans</i>	MAE	[aC ₁ im]Cl, [C ₂ C ₁ im][C ₁ CO ₂], [C ₄ C ₁ im]Br, [C ₄ C ₁ im]Cl (pure IL) ^{71,72}
	<i>Illicium verum</i> and <i>Cuminum cyminum</i>		[C ₆ C ₁ im][PF ₆] (pure IL) ⁷³
	<i>Rosmarinus officinalis</i> (rosemary)		[C ₁₀ C ₁ im]Br, [C ₂ C ₁ im]Br, [C ₄ C ₁ im][BF ₄], [C ₄ C ₁ im][NO ₃], [C ₄ C ₁ im]Br, [C ₄ C ₁ im]Cl, [C ₆ C ₁ im]Br, [C ₈ C ₁ im]Br (water) ⁵⁵
	<i>Schisandra chinensis</i>		[C ₁₀ C ₁ im]Br, [C ₁₂ C ₁ im]Br, [C ₂ C ₁ im]Br, [C ₄ C ₁ im][BF ₄], [C ₄ C ₁ im][C ₁ CO ₂], [C ₄ C ₁ im][ClO ₄], [C ₄ C ₁ im][HSO ₄], [C ₄ C ₁ im][NO ₃], [C ₄ C ₁ im][OH], [C ₄ C ₁ im]Br, [C ₄ C ₁ im]Cl, [C ₆ C ₁ im]Br, [C ₈ C ₁ im]Br (water) ⁶⁵
Gallotannins	<i>Galla chinensis</i>	UMAE	[C ₄ C ₁ im][BF ₄], [C ₄ C ₁ im]Cl, [C ₄ C ₁ im]Br (water) ⁷⁴
Suberin	<i>Quercus suber</i> L. (cork)	SLE	[C ₂ C ₁ im][C ₂ OCO ₂], [C ₂ C ₁ im][C ₁ CO ₂], [C ₂ C ₁ im]Cl, [C ₄ C ₁ im]Cl, [N _{111(20H)}][C ₃ CO ₂], [N _{111(20H)}][C ₅ CO ₂], [N _{111(20H)}][C ₃ CO ₂], [N _{111(20H)}][C ₁ CO ₂], [N _{111(20H)}][C ₂ OCO ₂], ⁷⁵ [C ₂ C ₁ im][C ₅ CO ₂], [N _{111(20H)}][C ₅ CO ₂], [N _{111(20H)}][C ₇ CO ₂], [N _{111(20H)}][C ₉ CO ₂] (pure IL) ⁷⁶
Saponins	<i>Ilex paraguariensis</i> , <i>Aquifoliaceae</i> (mate) and		[aC ₁ im]Cl, [C ₂ C ₁ im][C ₂ OCO ₂], [C ₂ C ₁ im][CF ₃ SO ₃], [C ₂ C ₁ im][C ₂ SO ₄], [C ₂ C ₁ im][C ₁ CO ₂], [C ₂ C ₁ im][N(CN) ₂], [C ₂ C ₁ im]Cl, [C ₄ C ₁ im]Cl, [C ₆ C ₁ im]Cl, [C ₇ H ₇ C ₁ im]Cl, [C ₈ C ₁ im]Cl, [N _{111(20H)}][Ntf ₂], [N _{111(20H)}]Cl, [(OH)C ₂ C ₁ im]Cl (water) ⁷⁷
Polyphenols	<i>Camellia sinensis</i> , Theaceae (tea)		
Para Red Sudan (I, II, III and IV)	Chilli powder and chilli oil		[C ₄ C ₁ im][PF ₆], [C ₆ C ₁ im][PF ₆] (pure ILs) ⁷⁸

Gallotannins are a type of hydrolysable tannins formed when gallic acid esterifies and binds with the hydroxyl group of a carbohydrate such as glucose. These compounds are the major constituents of *Galla chinensis* and present several biological and pharmacological properties.⁷⁴ Powered by previous works^{122,123}, in which the ultrasound/microwave-assisted extraction (UMAE) was used for the extraction of value-added compounds from natural sources, Lu et al.⁷⁴ proposed the application of this technique for the extraction of gallotannins from *Galla chinensis*. Furthermore, the authors⁷⁴ studied the substitution of organic solvents in UMAE with the following ILs: [C₄C₁im][BF₄], [C₄C₁im]Br and [C₄C₁im]Cl. The optimum UMAE conditions found are as follows: 2.5 mol/L of [C₄C₁im]Br, ultrasonic power of 50 W, microwave irradiation power of 400 W, 1 min of extraction and a solid-liquid ratio of 1:15.⁷⁴ Fig. 14 confirms the authors results supporting the highest extraction yields attained with IL-based UMAE.⁷⁴ Furthermore, the extraction time was considerably reduced from 6 h to 1 min.⁷⁴ As proposed by the authors,⁷⁴ this improved performance seems to be driven by a synergistic effect between ultrasonic- and microwave-based extractions: (i) microwave heating allows a higher heat and mass transfer that is not attained when conventional heating is used; and (ii) the application of ultrasounds during the extraction process intensifies the mass transfer and the biomass cells disruption which permit a better solvent penetration and capillary effects.⁷⁴ Moreover, with the addition of an IL, this increase in performance is amplified, as depicted in Fig. 14, making of IL-UMAE a powerful extraction technique.

The similarities between suberin and other lignocellulosic materials suggest that it could be soluble in tailor-made ILs. In this context, Garcia et al.⁷⁵ proposed the use of ILs for the dissolution of suberin domains from cork biopolymers. Suberin is

**Fig. 14** Yield of gallotannins extraction from *Galla chinensis* with different extraction techniques.⁷⁴

a cross-linked polymer composed of aromatic and aliphatic domains. Beyond all the potential applications of cork, its major component, suberin, is a valuable source of property-enhancing additives.¹²⁴ Garcia et al.⁷⁵ investigated a large number of ILs for the dissolution/extraction of suberin from cork (cf. Table 8) while taking into account their toxicological and biodegradation features.⁷⁵ After the refined cork dissolution in ILs, Attenuated Total Reflectance Fourier Transform Infrared (ATR-FTIR) spectroscopy was used for the characterization of cork and for the

qualitative assessment on the dissolution process.⁷⁵ It was observed that [C₂C₁im]Cl and [C₄C₁im]Cl were not able to dissolve significant amounts of refined cork.⁷⁵ However, when the Cl⁻ anion was substituted by [C₂OCO₂]⁻ or [C₁CO₂]⁻, the dissolution efficiency significantly increases.⁷⁵ Nevertheless, cholinium-based ILs revealed an even greater performance than their imidazolium-based counterparts, particularly on the dissolution of the aromatic components of suberin. The increase of the alkyl chain length at the anion, in [C_nCO₂]⁻, led also to a favourable effect on the dissolution of suberin – due to an increase on the anion basicity as explained by the authors.⁷⁵ Finally, Garcia et al.⁷⁵ showed that the employed cholinium-based ILs exhibit very low inhibitory capacities. The biodegradation of the [C₅CO₂]⁻ anion was also confirmed by ¹H NMR spectroscopy. Consequently, the biocompatible and biodegradable nature of [N_{111(2OH)}][C₅CO₂]⁻ coupled to its high ability to dissolve refined cork supports the development of a more environmentally-friendly and effective process. Later, the same researchers reported the detailed chemical and structural characterisation of the extracted suberinic material.⁷⁶ The ILs ability to extract suberin domains from cork was as follow: [C₂C₁im][C₅CO₂]⁻ (30 %) < [N_{111(2OH)}][C₉CO₂]⁻ (59 %) < [N_{111(2OH)}][C₇CO₂]⁻ (64 %) < [N_{111(2OH)}][C₅CO₂]⁻ (67 %).⁷⁶ The different extraction efficiencies obtained with the ILs [C₂C₁im][C₅CO₂]⁻ and [N_{111(2OH)}][C₅CO₂]⁻ undoubtedly confirm the cholinium cation role on the suberin extraction.⁷⁶ The authors suggested that the strong interactions occurring between the carboxylate moiety of the anion and the imidazolium ring partially block the suberin extraction from cork.⁷⁶

Ilex paraguariensis (mate) and *Camellia sinensis* (tea) have numerous bioactive compounds in their composition, and which are responsible for their human health benefits. Polyphenols and saponins are examples of compounds present in tea and mate. To overcome the major drawbacks of the traditional extraction methods, Ribeiro et al.⁷⁷ applied IL aqueous solutions as major solvents for the SLE of polyphenols and saponins from both leaves and aerial parts of mate and tea. The influence of several parameters, such as the IL chemical structure, water content, solid-liquid ratio, temperature, and contact time were also ascertained.⁷⁷ In general, higher extraction yields of saponins were obtained from tea when compared to mate. The extraction ability of 14 ILs was analysed and [C₇H₇C₁im]Cl presented the best performance for both substrates.⁷⁷ These results can be explained based on the favourable π···π interactions that exist between the “extra” aromatic group at the imidazolium cation and the aglycone group in saponins. The effect of the alkyl chain length in imidazolium-based ILs was also investigated and showed to be more relevant in the saponins extraction from mate.⁷⁷ In general, the increase of the cation alkyl chain length leads to a decrease on the extraction efficiencies.⁷⁷ The analysis of the presence of functional groups at the cation was also performed, and the authors concluded that more polar ILs have a favourable effect on the extraction of tea saponins while the opposite was observed for mate saponins.⁷⁷ For imidazolium-based ILs, the IL anion has no significant effect on the saponins extraction while with cholinium-based ILs, the chloride anion leads to higher extraction efficiencies.⁷⁷

Ribeiro et al.⁷⁷ also studied the ability of several ILs for the

extraction of phenolic compounds from *Ilex paraguariensis* and *Camellia sinensis*. Generally, lower extraction efficiencies were found when compared with saponins.⁷⁷ The ILs [C₂C₁im]Cl and [N_{111(2OH)}]⁺Cl⁻ led to the highest extraction yields while the [C₇H₇C₁im]Cl was the poorest IL in the extraction of phenolic compounds.⁷⁷ Ribeiro et al.⁷⁷ concluded that [N_{111(2OH)}]⁺Cl⁻ was the best option as solvent for the extraction of saponins and phenolic compounds, either from mate or tea. Additionally to the remarkable extraction efficiencies, the choline chloride ([N_{111(2OH)}]⁺Cl⁻) is an essential nutrient, which can be extracted from biomass, and is a part of the B-complex of vitamins, and thus it is nontoxic, biodegradable, and environmentally friendly. [N_{111(2OH)}]⁺Cl⁻ was further used to optimize the conditions of the extractive process by a central composite experimental design.⁷⁷ Temperature has no significant effect on the extraction of saponins and phenolic compounds. Extraction efficiencies of mate saponins around 70 % were obtained with [N_{111(2OH)}]⁺Cl⁻ after 4 h of extraction.⁷⁷

Plants are also an excellent source of other types of compounds with a wide variety of interesting applications, such as natural dyes. Sudan dyes are commonly used as colouring additives in the manufacturing of some products, such as wax, textile, and floor.¹²⁵ With the intention of determining Sudan dyes in foods, HPLC has been widely employed.¹²⁶⁻¹³² However, the sample pre-treatment is always required and using toxic VOCs.¹³¹ In order to overcome this problem, in 2009, Fan et al.⁷⁸ reported a new simple analytical method, based on the coupling of an IL-based SLE with HPLC, for the determination of Sudan dyes (I, II, III and IV) and Para Red in chilli powder, chilli oil and also in food additive samples. Two different ILs were studied ([C₄C₁im][PF₆]⁻ and [C₈C₁im][PF₆]⁻) and the IL volume and extraction time effects were also established.⁷⁸ The higher extraction efficiencies were attained with pure [C₈C₁im][PF₆]⁻ which support the role of dispersive interactions occurring between those highly hydrophobic dyes and the IL. Note that the octanol-water partition coefficients of these dyes vary between 3.2×10⁵ and 5.0×10⁸.⁹⁷ Moreover, the extraction recoveries of the five dyes increased with the extraction time (10–40 min for chilli powder and 10–20 min for chilli oil).⁷⁸ Fan et al.⁷⁸ also compared the extraction efficiencies obtained with [C₈C₁im][PF₆]⁻ with those obtained with acetonitrile, which is usually used in the extraction of Sudan dyes. The extraction recoveries obtained with the IL were significantly higher than those obtained with the molecular solvent, except for the Para Red extracted from the chili oil matrix and where the extractions recoveries were similar.⁷⁸ Finally, the authors applied the proposed method to real food samples – chili powder, chili oil and food additives. The recoveries obtained varied between 77-110 % in chili powder, 71-108 % in chili oils and 71-107 % in food additives.⁷⁸

Lipids extraction from microalgae

In the last decades, due to a fast increase on energy consumption, with the decrease and unstable supply of petroleum and the global warming intensification, we have been facing an amplified interest into renewable energy sources. Nowadays, most biodiesel is derived from edible vegetable oils, such as palm, rapeseed and soybean oils, via a transesterification reaction. Nonetheless, the growing demand for food supplies do not allows the exploitation of agricultural products in a large scale for energy production.

The high abundance of microalgae, high photosynthetic efficiency and high production rates are key points that ruled their exploitation towards the production of biodiesel.¹³³ Furthermore, lipids, which can represent more than 20% of microalgae dry weight, are the most valuable fraction since they represent high energy contents and similar to conventional fuels.

Lipids are usually extracted from algae biomass by Soxhlet extraction and by the Bligh and Dyer's method.¹³⁴ Though, and as discussed previously, the application of organic solvents leads to health and environmental concerns. Thus, between 2010 and the end of 2013, a total of five articles were published⁷⁹⁻⁸³ proposing the application of ILs as extraction solvents of value-added compounds from microalgae by simple SLE^{79-81,83} or UAE.⁸² All the aquatic biomass sources and pure ILs or ILs solutions used as solvents in the lipids extraction are listed in Table 9.

Young et al.⁷⁹ reported the good performance of [C₂C₁im][C₁SO₄]-methanol solutions for the dissolution of biomass and extraction of lipids from *Chlorella* microalgae. Later, Kim et al.⁸⁰ investigated the IL cation and anion effects on the lipids extraction efficiency. In this work,⁸⁰ it was possible to conclude that the lipids extraction is mainly driven by the IL anion nature and that hydrophilic ILs are the most favorable for the target extraction.⁸⁰ [C₄C₁im][CF₃SO₃], [C₄C₁im][C₁SO₄] and [C₂C₁im][C₁SO₄] presented the best extraction results (125.4, 118.4 and 118.8 mg/g of dried weight, respectively) compared with the commonly applied method of Bligh and Dyer (106.2 mg/g of dried weight).⁸⁰ On the other hand, Malihan et al.⁸³ provided more emphasis into the sugars extraction, such as the polysaccharide laminara, although they also reported the extraction of lipids from brown algae. In this work, several mineral acids were tested as catalysts together with [C₄C₁im]Cl, and where the combination [C₄C₁im]Cl/HCl dictated the higher extraction performances observed for carbohydrates.⁸³

Recently, Kim et al.⁸² suggested a new method for the extraction of lipids extraction using IL-based UAE. In this work, the following results were observed: (i) 21 and 29 mg of lipids per g of dried weight were obtained by Soxhlet and the Bligh and Dyer's method, respectively; (ii) 47 mg/g were attained when [C₄C₁im][C₁SO₄] was used; and (iii) the amount of lipids extracted using [C₄C₁im][C₁SO₄] was 1.6 times higher making use of UAE (75 mg/g).⁸² Moreover, the IL-based UAE process drastically decreases the time of extraction.⁸²

In the end of 2013, Choi et al.⁸¹ proposed a different approach by mixing salts with ILs envisaging the extraction of lipids from microalgae. The authors⁸¹ observed that these mixtures display a better performance than their singular compounds due to synergetic effects. The mixture composed of FeCl₃·6H₂O and [C₂C₁im][C₁CO₂] led to an extraction yield of lipids of 227.6 mg/g (compared against the 113.0 and 218.7 mg/g obtained with the pure compounds).⁸¹ Moreover, at the optimum conditions identified by the authors (FeCl₃·6H₂O/[C₂C₁im][C₁CO₂] ratio of 5:1, 90 °C and 1h of extraction time) the fatty acids content of the extracted lipids was 981.7 mg/g, with less than 2 % of impurities.⁸¹

Isolation of extracted value-added compounds

Despite the well-established good performance of ILs in the extraction of value-added compounds from biomass, the

Table 9 List of aquatic biomass sources, ILs or ILs solutions (the molecular solvent is presented between parentheses) used and different extraction techniques employed in lipids extraction.

Natural extract	Method	IL
<i>Chlorella vulgaris</i>	SLE	[C ₂ C ₁ im][C ₁ SO ₄] (methanol) ⁷⁹
		[C ₄ C ₁ im][CF ₃ SO ₃], [C ₄ C ₁ im][C ₁ SO ₄], [C ₄ C ₁ im][C ₁ SO ₃], [C ₄ C ₁ im][BF ₄], [C ₄ C ₁ im][PF ₆], [C ₄ C ₁ im][Ntf ₂], [C ₄ C ₁ im]Cl, [C ₂ C ₁ im][C ₁ SO ₄], [C ₂ C ₁ im]Cl, [C ₂ C ₁ im]Br, [C ₂ C ₁ im][C ₁ CO ₂] (methanol) ⁸⁰
	UAE	[C ₂ C ₁ im][C ₁ CO ₂], [C ₂ C ₁ im][HSO ₄], [C ₂ C ₁ im][(C ₂) ₂ PO ₄], [C ₂ C ₁ im][SCN], [C ₂ C ₁ im][Ntf ₂] (pure IL or salt mixtures) ⁸¹
<i>Sargassum fulvellum</i> , <i>Laminaria japonica</i> and <i>Undaria pinnatifida</i>	SLE	[C ₄ C ₁ im]Cl (mineral acids) ⁸³
	UAE	[C ₄ C ₁ im][C ₁ SO ₄] (pure IL) ⁸²

isolation/purification of the target compounds from the IL-based solvent remains a challenge. This step is of crucial relevance when envisaging the scale-up of the extraction processes. Although IL-mediated extractions display a high performance, the non-volatile nature of the aprotic ILs represents a drawback because a simple evaporation cannot be applied to recover the high-value materials. Therefore, the development of alternative approaches requires the attention of researchers working on this field. Table 10 summarizes the isolation techniques already proposed by different authors. Nevertheless, it should be remarked that although a large amount of literature sources focused on the optimization of the extraction procedures, only less than half of the authors studied the possibility of isolating the valuable compounds from the final IL-based mixture/solution.^{41-43,50,51,59-63,67,69,71,72,74,76,77,135} The isolation methods most applied consist on back-extractions using organic solvents,^{41-43,63} evaporation of the solvents or compounds (when applicable)^{50,61,71,72} and precipitation with antisolvents.^{60,62,76} Less employed techniques, such as the use of a macroporous material^{74,141} and anion-exchange resins^{67,69}, were also proposed.

When dealing with volatile compounds, such as essential oils, the negligible vapor pressure of most ILs is a favorable property concerning the oils-IL isolation/separation. Most essential oils can be recovered by hydro-distillation (Fig. 15A) as proposed by Jiao et al.^{71,72} and Bica and co-workers⁶¹. After distillation and condensation, essential oils can be easily separated by decantation from water since they present a poor miscibility in the aqueous phase forming a biphasic system. Jiao et al.^{71,72} also recommended the application of microwaves to increase the performance of the hydro-distillation, while decreasing the time and energy consumption.

Apart from the essential oils, most value-added compounds extracted from biomass are not volatile. However, and aiming at making use of an evaporation process, protic ILs of high volatility can be applied as successfully demonstrated by Chowdhury et al.⁵⁰. However, this method is only viable if the IL

presents a high selectivity for the target compound; otherwise, more separation steps will be needed for the separation and purification of the valuable material from other co-extracted impurities.

5 A back-extraction stage with organic solvents is the most popular isolation technique to recover value-added compounds from the IL solution.^{41-43,63} Yet, this approach is only possible when the extracted compound displays a preferential affinity and partitioning for the second solvent (Fig. 15B). Non-water
10 miscible organic solvents are recurrently used since most of the reported extractions employed aqueous solutions of ILs. The valuable compounds are thus removed and recovered from the IL phase by a second liquid-liquid extraction step followed by the organic solvent evaporation. It should be remarked that this
15 approach requires the use of volatile and more hazardous organic solvents that ILs were supposed to replace. Nonetheless, if the IL-based extraction presents high extraction performances, and if the organic solvents are properly handled, recovered and reused, the final process can still be greener and sustainable. On the other
20 hand, and although not applied on any of the works reviewed in this manuscript, supercritical CO₂ can be foreseen as a potential alternative to the back-extraction and precipitation steps as suggested in literature.^{136,137} Supercritical CO₂ is amongst the
25 “green solvents” list and albeit it presents a limited polarity range, and because of that it is typically used combined with molecular solvents to tailor the solvent polarity and affinity for a given product, it can be considered here as the back-extraction and precipitating agent instead of the extraction solvent.

30 **Table 10** Isolation methods used in the recovery of the value-added compounds extracted from biomass.

Compounds family	Isolation method	IL recovery
Alkaloids	back-extraction with organic solvents ⁴¹⁻⁴³	✓
	IL distillation ⁵⁰	✓
Flavonoids	high-speed counter-current chromatography ⁵¹	✓
	solid-phase extraction ⁵⁹	✓
Terpenoids	Hydro-distillation ⁶¹	✓
	precipitation with water ^{60,62}	✓
Aromatic compounds	anion-exchange resin ^{67,69}	✓
	IL distillation ⁵⁰	✓
Natural mixtures	microwave hydro-distillation ^{71,72}	✓
	addition of a hydrophobic IL ⁷⁷	✗
	precipitation with water ⁷⁶	✓
Others	macroporous resin ^{74,135}	✓
	IL distillation ⁵⁰	✓
	back-extraction with organic solvents ⁶³	✓

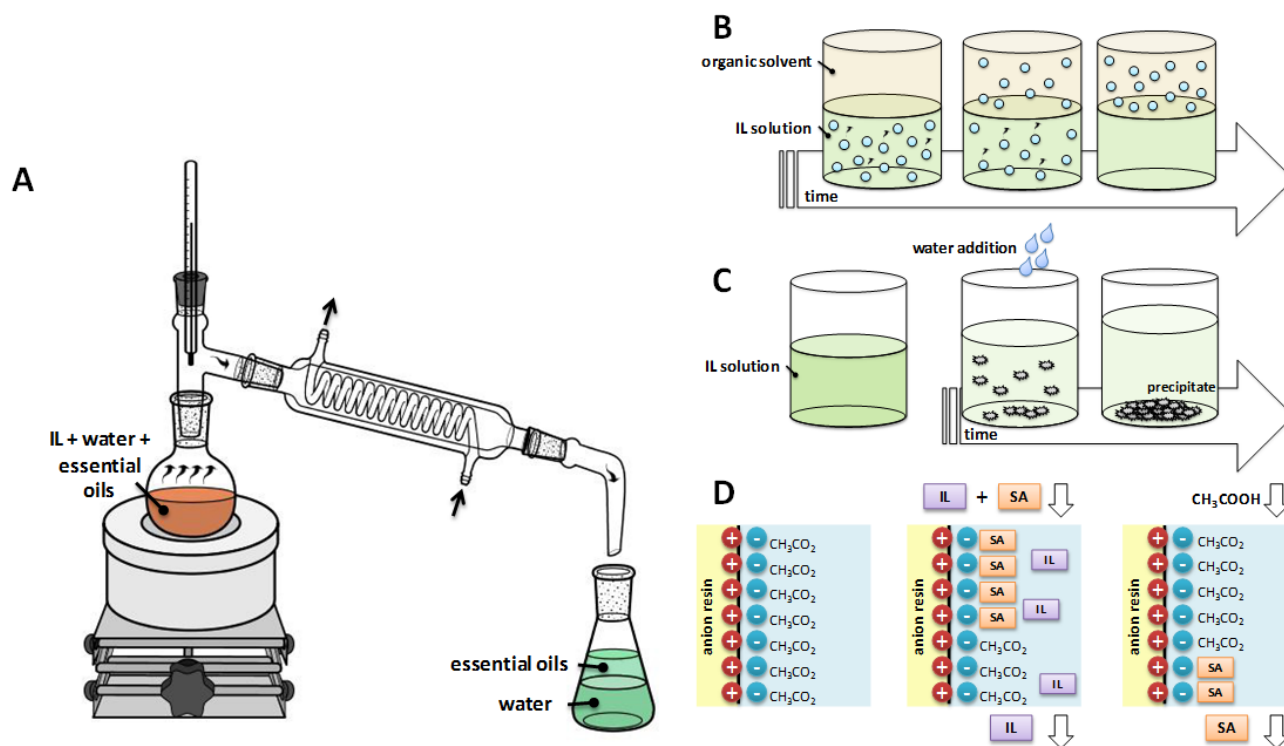


Fig. 15 Schematic representation of the methods proposed for the isolation of value-added compounds after the extraction with ILs or ILs solutions. A – hydro-distillation; B – back-extraction; C – precipitation with water; D – anion exchange resin.

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In addition to the previously described approaches, the isolation and recovery of non-volatile and highly hydrophilic compounds extracted with aprotic IL solutions is the most complex challenge. Aiming at finding viable and effective alternatives, Usuki et al.⁶⁹ and Zirbs et al.⁶⁷ proposed the use of an anion-exchange resin for the isolation of shikimic acid. As illustrated in Fig. 15D, the anion-exchange resin in the acetate form allows the loading of shikimic acid on the solid phase, while the IL is washed out with water and can be simple recovered by further water distillation. Through the loading of a diluted acetic acid solution the shikimic acid is then removed from the resin and can be isolated by consecutive separation steps.^{67,69}

A similar process was demonstrated by Lu et al.^{74,141} for the recovery of tannins and by Bi et al.⁵⁹ in the isolation of astaxanthin from shrimp waste using macroporous resins. Lu et al.^{74,141} used a polymer with high adsorption ability and polarity to selectively adsorb the target compound through electrostatic forces, hydrogen-bonding interactions, complexation and size sieving.^{138,139} Bi et al.⁵⁹ employed a molecularly imprinted polymer to take advantage on the cavity shape selectivity for the separation of the target component. Anion-exchange and macroporous resins, as well as molecularly imprinted materials, are excellent options since they can be washed and reused several times without losing their adsorption capability.

Sun et al.⁵¹ applied high-speed counter-current chromatography for the separation of isoflavones. In this case, a multi-step liquid-liquid extraction is engaged. With this technique the authors⁵¹ reported high purity factors of 95.3, 95.9 and 97.0 % for tectoridin, iristectorin B and iristectorin A, respectively, extracted from *Iris tectorum*. Unfortunately, the authors⁵¹ didn't evaluate the ILs recovery possibility.

All the methods reported before not only allow the isolation of the target compound but also permit the recovery and reuse of the IL (cf. Table 9) and represent a step forward in the development of more sustainable extraction methods.

Finally, Ribeiro et al.⁷⁷ suggested a completely different method for the recovery of saponins and polyphenols from the IL-rich aqueous phase of an aqueous biphasic system by the addition of a more hydrophobic IL ($[N_{111}(2OH)][Ntf_2]$). The goal is to remove the hydrophilic IL from the aqueous phase and to obtain a concentrated aqueous solution containing the saponins and polyphenolic compounds.⁷⁷ As major drawbacks, this approach doesn't completely remove the hydrophilic IL from the aqueous phase, it introduces a strong salting-out salt to create the aqueous biphasic system that intrinsically partitions (even if in a small extent) to the phase containing the valuable compounds, and turns more complex the IL recovery process since a mixture of ILs is formed.

Concerning the lipids recovery, no particular processes were suggested since these compounds are not soluble in the extraction solvents, occurring the formation of a lipid layer and another extraction solvent layer which easily allows their separation.^{79,80,82}

Economic and environmental analysis on the use of ILs as extraction solvents

After the demonstration of the outstanding potential of ILs as extraction solvents of value-added compounds from bioresources,

one major question arises: are these approaches economically competitive and more environmentally-benign than traditional methods which often employ VOCs? The lack of volatility in ILs is a major advance in the reduction of the environmental footprint. Nevertheless, and as discussed before, this negligible volatile nature afforded by ILs also turns more complex the isolation and recovery of the value-added compounds. Trying to overcome this issue some alternatives were already proposed and discussed in the previous section. On the other hand, a complete life cycle assessment of ILs' processes is crucial to support their suitability from a "greener" and sustainable perspective. For that purpose, the recovery and reusability of ILs and IL solutions are

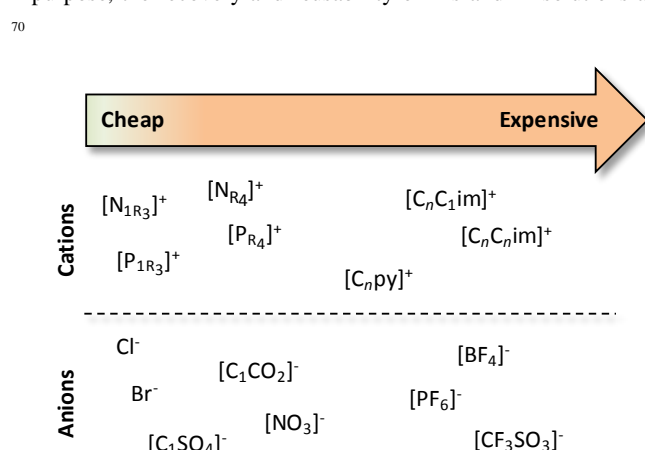


Fig. 16 Schematic illustration of the relative prices of ILs estimated based on the cost of the starting materials used in their synthesis.¹⁴⁰

vital issues both to support the economic viability and to minimize the environmental footprint of the proposed processes.

The high production costs associated to ILs recurrently create a large controversy on the viability of their application at an industrial scale. It is well known that the price of ILs is mainly dependent on the raw materials needed for their production and a rough estimation of their relative prices was already carried out and is presented in Fig. 16.^{140,141} The industrial price of some commodity, specialized solvents, along with the estimated cost of $[C_nC_1im]^+$ - and ammonium-based ILs is presented in Table 11. Quaternary ammonium- (including cholinium-) based ILs are less expensive than their imidazolium-based counterparts and surely deserve to be further investigated. Moreover, ILs composed of fluorinated anions are also more expensive and should be substituted by carboxylate- and halogen-based ones.

Even if researchers optimize the production processes for ILs, the price of an IL will be not comparable to that of a commodity solvent but it would be comparable to the higher end specialty chemicals. Nevertheless, it should be remarked that the ILs field is slowly moving away from imidazolium-based ILs into an era of cheaper and more environmentally benign ILs, such as carboxylate-, amino-acid-, carbohydrate- and cholinium-based ILs. Their raw materials are cheaper and obtained from renewable resources and much more work should be devoted to these alternatives. Other aspects should also be considered regarding the advantages of ILs over VOCs. It is well-known that the use of organic solvents has been restricted and strongly regulated by new legislations.¹⁴² Nowadays, the costs connected to the organic solvents application should also cover the costs associated to, and

for instance, personal protective equipment, emission control hardware and monitoring equipment. Thus, non-volatile compounds, such as ILs, present some advantages and should not be discarded based only on the price of the solvent. Furthermore, and particularly concerning the extraction of value-added compounds from natural resources, all the reported works here reviewed reveal that ILs are able to considerably increase the extraction efficiencies using, in general, high solid-liquid ratios (low amount of solvent), at lower temperatures (with organic solvents high temperatures are usually required in the common soxhlet extraction) and strongly reducing the operation time (from hours to few minutes). Even if microwave or ultrasound technologies are required, the increase on the extraction yield, the

Table 11 Industrial production price of some organic solvents and ILs.¹⁴³⁻¹⁴⁷

Organic Solvents / \$US		Ionic Liquids / \$US	
toluene	0.74 - 1.05 /L	[C _n C ₁ im]-based	14-34 /kg
ethanol	0.82 - 0.98 /L	[C ₁ im][HSO ₄]	2.96-5.88 /kg
methanol	0.25 - 0.54 /L	[N ₂₂₂₀][HSO ₄] ^d	1.24 /kg
acetonitrile	1.06 - 1.12 /kg	[N _{111(20H)}]Cl	1.21 /kg
<i>n</i> -butyl acetate	1.48 - 1.59 /kg	[N ₍₁₀₎₍₁₀₎₁₁]Cl ^e	8.71 /kg
chloroform	0.53 - 1.04 /kg	[N _{11(13)(C7H7)}]Cl ^e	5.28 /kg
ethylene glycols	1.43 /kg	[N _{1(20H)(TH)(TH)}][C ₁ SO ₄] ^f	2.27 /kg
<i>n</i> -methyl pyrrolidone	4.08 - 4.19 /kg		
sulfolane	~3.7 /kg		

^a[N₂₂₂₀][HSO₄] - triethylammonium hydrogensulphate; [N₍₁₀₎₍₁₀₎₁₁]Cl - didecyldimethylammonium chloride; [N_{11(13)(C7H7)}]Cl - cocoalkonium chloride; [N_{1(20H)(TH)(TH)}][C₁SO₄] - dihydrogenated tallowylethyl hydroxyethylammonium methylsulphate.

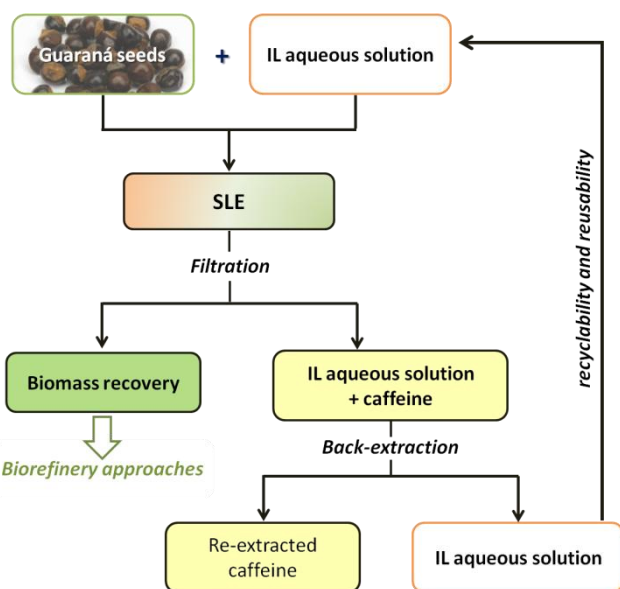


Fig. 17 Flowchart of the process used to extract caffeine from guaraná seeds.⁴²

reduction on the extraction time and the possibility of significantly reducing the environmental impact of the process, are excellent reasons to make of an IL-based methodology a viable process.

As stated before, the recovery and reusability of ILs and IL solutions are fundamental aspects to support the economic viability and to minimize the environmental footprint of the proposed processes. Although highly important, only 10 works, among all the articles reviewed in this work, explored this possibility.^{41-43,61-63,67,71,72,76} The authors^{41-43,61-63,67,71,72,76} demonstrated that, after the isolation of the target compounds, ILs can be easily and almost completely recovered and recycled without a significant loss on the value-added materials extraction efficiency. For instance, Coutinho and co-workers⁴² studied the recovery and reusability of the IL after the extraction of caffeine from *Paullinia cupana* (guaraná). After the back-extraction procedure, the IL aqueous solutions were recovered and reused, for at least three times, without losing the extraction and selective ability for caffeine.⁴² Fig. 17 depicts a flowchart of the process used in the extraction of caffeine while highlighting the solvents recyclability and reusability. The authors shown that aqueous solutions of ILs are superior alternatives for the selective extraction of caffeine from biomass samples and that these systems can be recycled and reused without a loss on their extraction performance.⁴²

Considering a scale-up of the proposed methodologies to treat circa 50 kg of biomass, values such as 50 to 200 kg of IL in aqueous solutions are required (taking into consideration a solid-liquid ratio of 1:10 and an IL concentration between 0.5 and 2 M as usual optimized parameters). If pure ILs are used instead, 100-500 kg of IL are needed (considering a solid-liquid ratio between 1:2 and 1:10). Therefore, the recyclability studies are of foremost importance and only with their attempt ILs can be foreseen as industrial-scale solvents for application in the extraction of value-added compounds from biomass.

We propose here a simplified relation for the return (R) associated to the extraction of a particular value-added compound when ILs are used as extraction solvents. In eq. 1 the return per kg of treated biomass is equal to the gain, defined by the extracted concentration of the target compound in the biomass (C_{prod}) times its price per kg ($\$_{prod}$) minus the cost associated to the biomass ($\$_{biom}$), and the extraction process that we assume to be proportional to the cost of the IL lost in each kg of biomass treated. The cost of the IL lost in the process is given by the volume of the IL needed to treat one kg of biomass (V_{IL}) times its price per kg ($\$_{IL}$) times the ratio of IL lost during the recycling approach ($r_{IL\ lost}$). The factor α represents the proportional costs of the process and the non-proportional constant β represents other constant costs.

$$R = [C_{prod} \times \$_{prod} - \$_{biom}] - [V_{IL} \times \$_{IL} \times r_{IL\ lost} \times \alpha + \beta] \quad (1)$$

Through the application of eq. 1 it is possible to understand which variables represent a more relevant impact on the return of a given process allowing a quick, albeit superficial, evaluation of its economic viability. For instance, considering a volume of 3 L/kg_{biom}, an IL price of 20 \$/L and a recovery of 99 % ($r_{IL\ lost} =$

1%), in Fig. 18 it is possible to see a linear relationship between these two variables if a negligible cost of the biomass is assumed ($\$_{biom}=0$). In fact, the concentration of the extracted target compound is the main responsible for the product price. Small concentrations (in order of 1 wt %) represent small slopes which means that, for an input of for instance of $1\$/kg_{biom}$ in the return, the price of the value added-compound needs to increase $100\$/kg_{prod}$. However, if the concentration of the extracted compound increases 10 times the slope increases considerably. Moreover, at higher concentration values, the final price of the value-added compound is not considerably affected by the increase of the process cost (increase of α).

Through this economical analysis is possible to conclude that the application of ILs as extraction solvents is only viable when the concentration of extracted compounds is considerably high (> 5 wt %), or when they are truly high value-added compounds. For example, the viability of lipids extraction from microalgae is supported only by the high concentration of the target compounds on the biomass source. Nevertheless, and as discussed above, it is mandatory to have in consideration several other factors and a specific economic and environmental analysis should be carried out beforehand for each individual process.

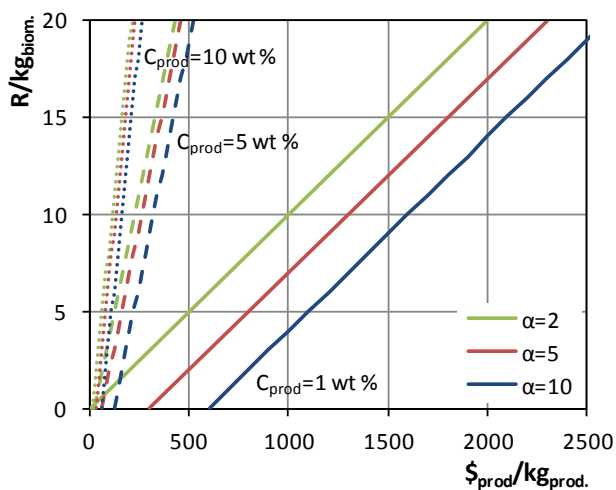


Fig. 18 Return obtained for each kg of treated biomass as a function of the value-added compounds cost.

Conclusions

Based on this literature review it is clear that ILs can be tailored for the extraction of target chemicals. In any dissolution process the interactions between solutes and solvents are a driving force in the extraction process. Hydrogen-bonding, $\pi\cdots\pi$, van der Waals and coulombic interactions have shown to effectively characterize the complex multiple interactions occurring between the natural value-added products and the IL solvent. Moreover, it was shown that the IL efficiency in destroying the cell walls, aiming at reaching the compound of interest for further solvation, plays a crucial role. The application of IL-based MAE and UAE results in an outstanding extraction performance and with a substantial reduction in the extraction time. In MAE, the direct interaction of the microwaves with the IL solution and free molecular water present in cells rules their rupture and the release of intracellular products into the solvent. ILs improve the transfer

of energy from the microwaves to the sample, increasing the speed of energy transfer and thus the extraction efficiency.

Based on the compiled results, three main IL-based solvents were applied: (i) pure ILs; (ii) IL aqueous solutions; and (iii) IL-alcohol mixtures. At this point, it is clear that the nature of the target compound guides the choice of the extraction solvent. Still, some major issues should be taken into account when choosing the solvent. For instance, pure ILs are only viable when they are liquid at room temperature and present low viscosities. Otherwise the extraction efficiencies will be low due to limited mass transfer coefficients and to the poor penetration of the ILs into the biomass structure. In addition, high temperatures are always required when working with pure ILs either to overcome their melting points or to reduce their viscosities and which represent further economic concerns. These problems can be overcome by the addition of water (the greenest of solvents) that reduces the viscosity and allows the extraction process to occur at low temperatures. Besides the lower energy consumption there is also a reduction on the overall cost of the solvent. The presence of water as the main constituent of the extraction solution can also prevent some problems with the thermal degradation of some value-added compounds. In summary, whenever possible, IL aqueous solutions should be the preferred choice.

It is also important to mention that some fluorinated-based ILs are not water-stable. In the presence of water some of these ILs suffer hydrolysis and form hydrofluoric acid. This reaction leads to adverse effects either in the degradation of the target biomolecule or in the IL irreversibly lost. Even thus, $[C_nC_{1m}][BF_4]$ -based ILs are the most studied ILs in aqueous solutions. This is a trend that needs to be urgently contradicted.

ILs have been claimed as “green” solvents, but this classification depends on the ions selected to create a given IL. A detailed life cycle assessment on new ILs for a certain application is strictly necessary in order to claim their suitability from a “greener” point of view. The search for more environmentally-benign ILs for extraction purposes is still in its infancy. Promising results were found on the use of ILs for the extraction of value-added compounds from natural sources. ILs were shown successful in the extraction of alkaloids, terpenoids, flavonoids, natural dyes, lipids, among others. However, the field of separation technology is still far from being fully developed or explored. More extensive studies on more benign ILs, such as ILs created from natural products that have been developed, are required. Furthermore, the application of deeper eutectic solvents (DES), formed by two solid materials from renewable resources, particularly to replace pure ILs in the extraction of highly hydrophobic compounds, can be seen as an alternative choice.

After extraction, the crucial step consists on the product recovery and on the solvents recyclability aiming at developing a sustainable process. The lack of volatility of ILs makes it nearly impossible to directly concentrate the non-volatile value-added products. In fact, this is a major lacuna in literature since few researchers attempted this step. Although some methodologies have already been proposed, including the addition of anti-solvents, back-extraction and adsorption approaches, further work must be done on the recovery of compounds from these extracts. Only after the development of suitable methodologies, ILs can be reused several times thereby decreasing the cost and the

environmental footprint of the whole process.

Notes and references

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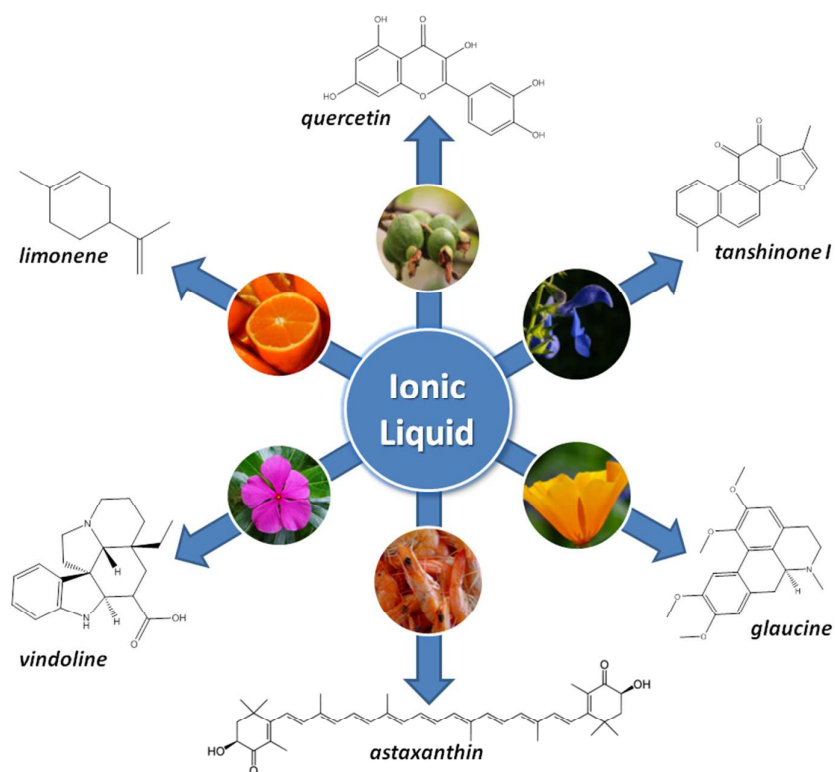
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Text

A literature's review and critical analysis on the use of ionic liquids for the extraction of value-added compounds from biomass.