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Ionic liquid solutions as extractive solvents for value-added compounds from biomass

Helena Passos, Mara G. Freire* and João A. P. Coutinho

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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 IL 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* the extraction performance of IL-based methodologies was also carried out and is here presented and discussed.

Introduction

In the past few decades, the word "green" acquired a new meaning in chemistry-related fields. The introduction of the twelve principles of green chemistry played a major role in the development of "green engineering"[1] and the importance of sustainable development and "green chemistry" changed the

Departamento de Química, CICECO, Universidade de Aveiro, 3810-193 Aveiro, Portugal. E-mail: maragfreire@ua.pt; Fax: +351 234370084; Tel: +351 234370200

Helena Passos

Helena Passos was born in 1989 in Viana do Castelo, Portugal. She obtained her MSc degree in Chemical Engineering from the University of Aveiro, Portugal, in 2012, and she is currently a PhD student in Chemical Engineering at the same University, working on the development of new platforms for the extraction and separation of bioactive compounds using ionic liquids.

Mara G. Freire

Mara G. Freire received her PhD degree in 2007 in Chemical Engineering from the University of Aveiro, Portugal. From 2008 to 2013 she was a post-doctoral researcher at Instituto de Tecnologia Química e Biológica, ITQB2, the New University of Lisbon, Portugal. Since the beginning of 2014 she is a Coordinator Researcher at CICECO, at the Chemistry Department of University of Aveiro, and the principal investigator of a European Research Council (ERC) Starting Grant regarding the development of cost-effective purification platforms for biopharmaceuticals using ionic liquids.

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 CO_2, 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 ($[C_1CO_2]^-$), hexafluorophosphate ($[PF_6]^-$) and tetrafluoroborate ($[BF_4]^-$). However, the development of novel ILs is moving away from the more hydrophobic and fluorinated anions ($[PF_6]^-$, $[BF_4]^-$, *etc.*) towards less toxic and biodegradable alternatives, namely derivatives from carboxylic acids and amino-acid-based anions.[13,14] The search for 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 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.

João A. P. Coutinho

João A. P. Coutinho is a Full Professor at the Chemistry Department of University of Aveiro, Portugal, where he is the director of the Sustainability and Health Research Line at CICECO Laboratory. He studied Thermodynamics and Petroleum Technology at the Technical University of Denmark where he got his PhD in Chemical Engineering in 1995. Since 1997 he has been leading a multidisciplinary research team that focuses on a range of different subjects from the petroleum production in non-conventional reservoirs to the production and formulation of biofuels, and the development of novel separation processes for the biorefinery. Currently he strives to apply ionic liquids to these processes and is trying to better understand their physico-chemical behaviour for that purpose.

IL solutions as extractive solvents

In the past few years, the discrimination between natural and synthetic products has received 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 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 authors[39] demonstrated the successful application of IL 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]

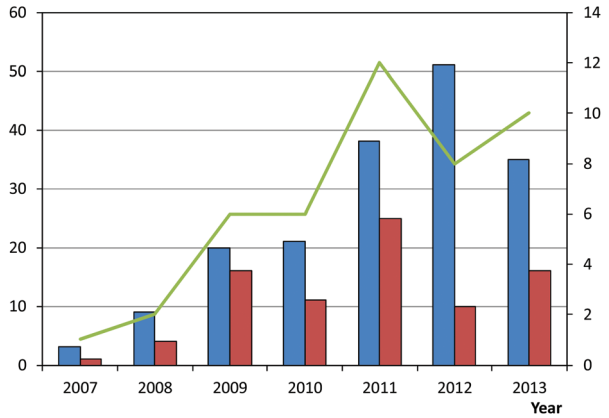


Fig. 1 ILs as solvents for the extraction of value-added compounds. Data from 2007 to 2013: number of articles per year (green line, secondary scale); number of ILs studied (blue bars, primary scale); and number of extracted value-added compounds (red bars, primary scale).

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 (5 articles) were also addressed although in a scarcer number of reports.[39–83]

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

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	*N*,*N*-Dimethyl(cyanoethyl)ammonium	$[N_{11(3N)0}]^+$	xii	Hexafluorophosphate	$[PF_6]^-$
xiii	2-(Dodecyloxy)-*N*,*N*,*N*-trimethyl-2-oxoethanaminium	$[N_{111(C2O(O)C12)}]^+$	xiii	Tosylate	$[Tos]^-$
xiv	*N*,*N*-Dimethylammonium	$[N_{1100}]^+$	xiv	Saccharinate	$[Sac]^-$
xv	Cholinium	$[N_{111(2OH)}]^+$	xv	Dimethylcarbamate	$[N(C_1)_2CO_2]^-$
xvi	*N*,*N*-Dimethylethanolammonium	$[N_{11(2OH)0}]^+$	xvi	Sulphate	$[SO_4]^-$
xvii	*N*,*N*-Dimethyl-*N*-(2-hydroxyethoxyethyl)ammonium	$[N_{11(2(O)2OH)0}]^+$	xvii	Hydrogenosulphate	$[HSO_4]^-$
xviii	*N*,*N*-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	$[C_{i3}CO_2]^-$
			xxv	Alkylcarboxylate	$[C_nCO_2]^-$

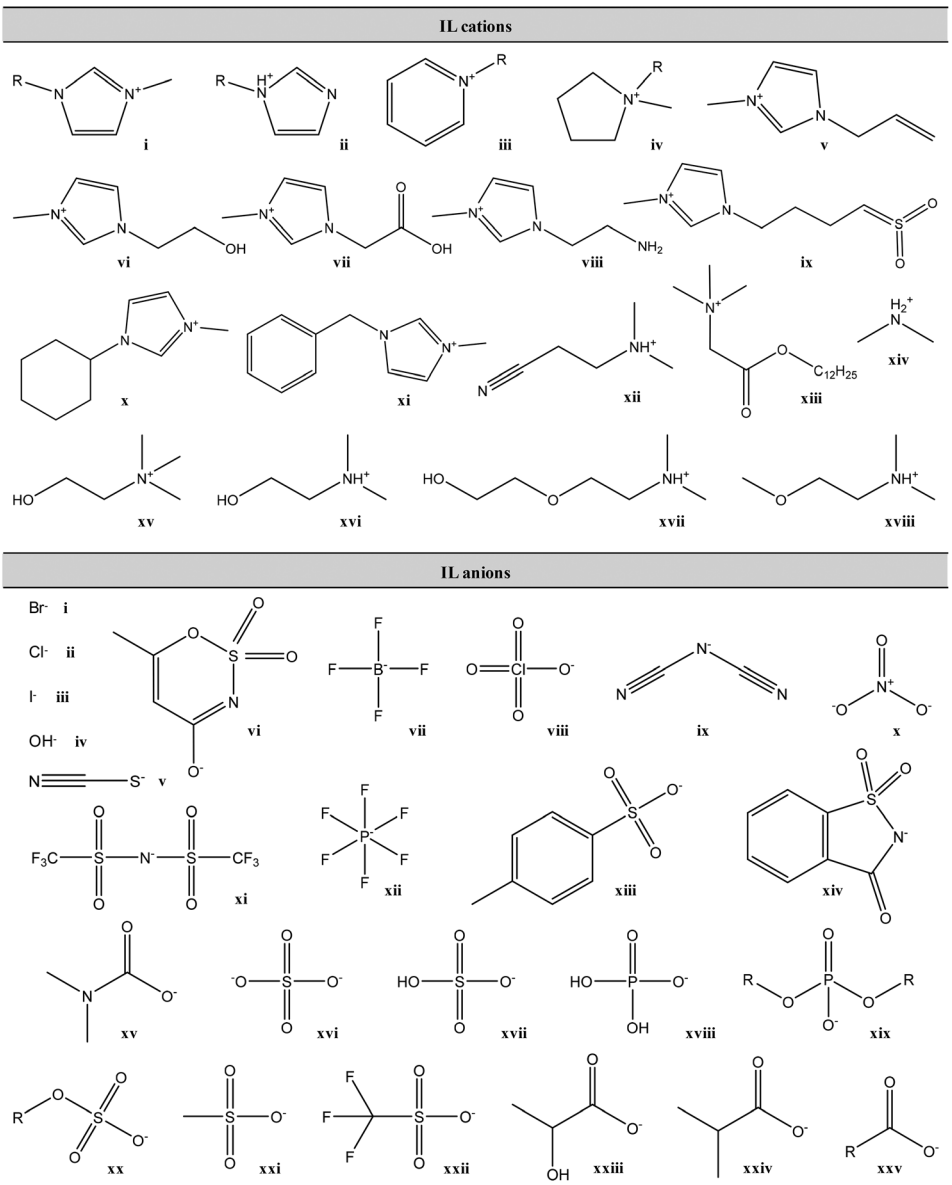


Fig. 2 Chemical structure of each IL cation and anion employed in the extraction of value-added compounds from natural sources. The nomenclature of each ion is presented in Table 1.

Fig. 3 depicts the usage frequency of the distinct cation–anion combinations. 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 $[C_4C_1im][Ace]$, $[N_{111(C2O(O)C12)}]Cl$, $[N_{1100}][N(C_1)_2CO_2]$, $[N_{11(3N)0}][C_2CO_2]$, $[N_{11[2(O)2OH]0}][C_2CO_2]$ 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 these SLE were coupled to MAE and ultrasound-assisted extraction (UAE) aiming at reaching higher extraction yields, and which embody more than two-third 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,

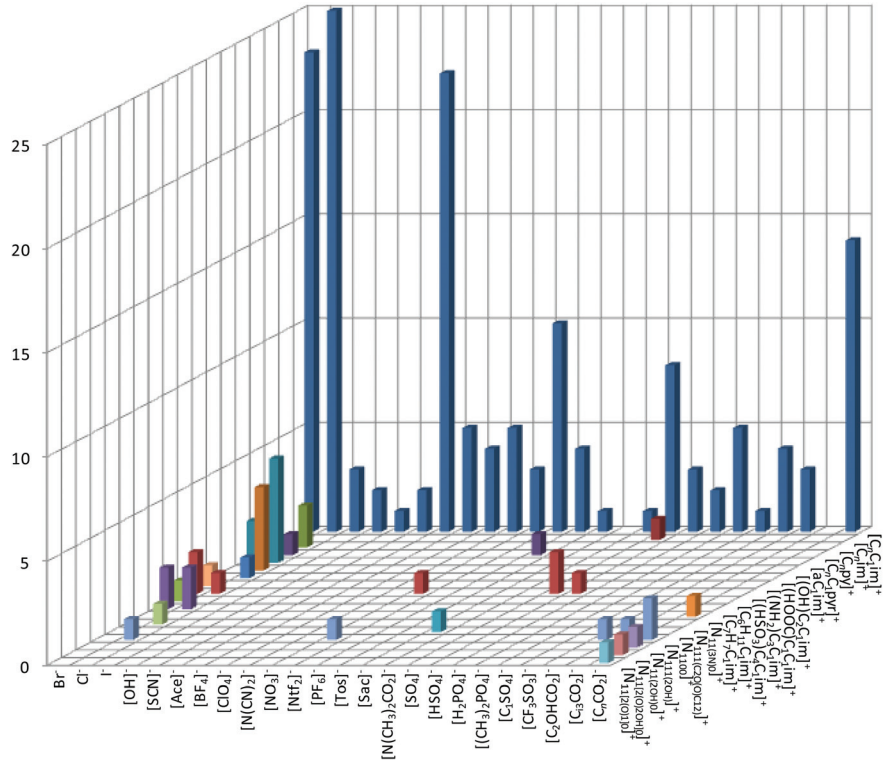


Fig. 3 Graphical representation of the available data on ILs as extractive solvents and as a function of different ions combinations.

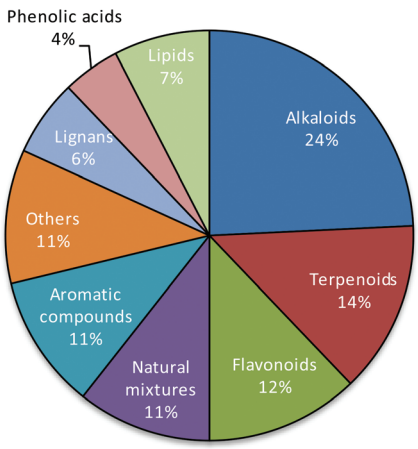


Fig. 4 Fraction of each family of natural compounds extracted from natural sources using ILs or IL solutions.

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 into different sections regarding independent natural compound 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.

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 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

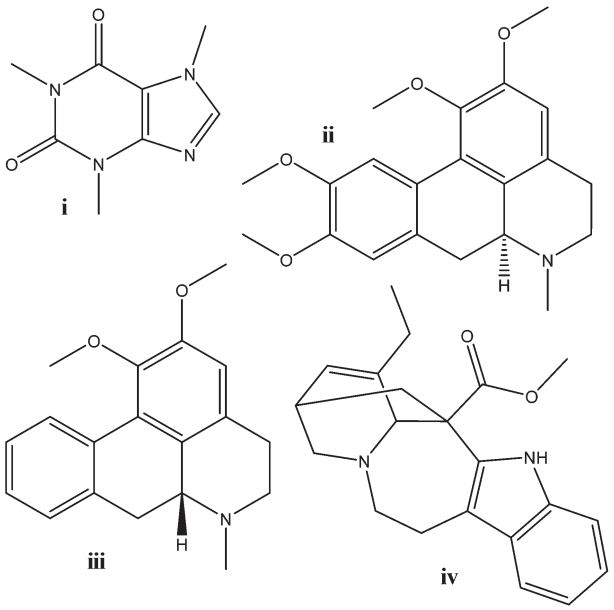


Fig. 5 Chemical structure of common alkaloids: (i) caffeine; (ii) glaucine; (iii) nuciferin; (iv) catharanthine.

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 coworkers[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

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

Value-added compound	Natural source	Technique	IL
Glaucine	*Glaucium flavum* (papaveraceae)	SLE	$[C_4C_1im][Ace]$, $[C_{10}C_1im][Ace]$, $[C_6C_1im][Ace]$, $[C_8C_1im][Ace]$, $[C_4C_1im][Sac]$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$ (water)[40,41]
Caffeine	*Paullinia cupana* (guaraná)		$[C_2C_1im]Cl$, $[C_2C_1im][C_1CO_2]$, $[C_4C_1im]Cl$, $[C_4C_1im][Tos]$, $[C_4C_1pyr][Tos]$, $[(OH)C_2C_1im]Cl$ (water)[42]
Piperine	*Piper nigrum* (white and black pepper)		$[C_{10}C_1im]Cl$, $[C_{12}C_1im]Cl$, $[C_{12}C_1im]Br$, $[C_{12}C_1im][CF_3SO_3]$, $[C_{12}C_1im][C_1CO_2]$, $[C_{12}C_1im][N(CN)_2]$, $[C_{14}C_1im]Cl$, $[N_{111(C2O(O)C12}]Cl$ (water)[43]
		UAE	$[C_4C_1im][BF_4]$, $[C_4C_1im][H_2PO_4]$, $[C_4C_1im][PF_6]$, $[C_4C_1im]Br$, $[(HSO_3)C_4C_1im]Br$, $[C_6C_1im][BF_4]$ (water)[44]
10-Hydroxycamptothecin Camptothecin	*Camptotheca acuminata*		$[aC_1im]Br$, $[C_7H_7C_1im]Br$, $[C_2C_1im]Br$, $[C_3C_1im]Br$, $[C_4C_1im][BF_4]$, $[C_4C_1im][ClO_4]$, $[C_4C_1im][HSO_4]$, $[C_4C_1im][NO_3]$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$, $[C_6C_1im]Br$, $[C_8C_1im]Br$, $[C_6H_{11}C_1im]Br$ (water)[45]
Catharanthine Vinblastine Vindoline	*Catharanthus roseu*		$[aC_1im]Br$, $[C_2C_1im]Br$, $[C_4C_1im][BF_4]$, $[C_4C_1im][ClO_4]$, $[C_4C_1im][HSO_4]$, $[C_4C_1im][NO_3]$, $[C_4C_1im][Tos]$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$, $[C_4C_1im]I$, $[C_6C_1im]Br$, $[C_8C_1im]Br$ (water)[46]
Fangchinoline Tetrandrine	*Stephaniae tetrandrae*		$[C_4C_1im][BF_4]$ (water)[47]
Isoliensinine Liensinine Neferine	*Nelumbo nucifera* (lotus leaf)	MAE	$[C_2C_1im][BF_4]$, $[C_4C_1im][BF_4]$, $[C_4C_1im][PF_6]$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$, $[C_6C_1im][BF_4]$, $[C_8C_1im][BF_4]$ (water)[48]
Nuciferine *N*-Nornuciferine *O*-Nornuciferine			$[C_2C_1im]Br$, $[C_4C_1im][BF_4]$, $[C_4C_1im][PF_6]$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$, $[C_6C_1im]Br$, $[C_8C_1im]Br$ (water)[49]

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 $[C_4C_1im]^+$ cation coupled to the anions Cl^-, Br^-, $[BF_4]^-$ and $[PF_6]^-$ it was observed that $[C_4C_1im][BF_4]$ is the most efficient IL for the extraction of isoliensinine, liensinine and neferine.[48] On the other hand, $[C_4C_1im]Br$ 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] 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 2 h to 90 s). 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 roseu*; and Zhang *et al.*[47] used IL-based UAE to recover fangchinoline and tetrandrine from *Stephaniae tetrandrae*. In these works[44–47] 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 authors[44–47] 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 $[C_4C_1im]Br$ and $[C_4C_1im]Cl$, 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, $[C_6C_1im]Br$ and $[C_6H_{11}C_1im]Br$, 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 $[C_6C_1im]Br$ is more favourable for the alkaloids extraction.[45]

In general, all authors[44–47] 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 authors[47] 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 authors,[47] 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 G*lausium flavum*,[40,41] of caffeine from *Paullinia cupana* (guaraná seeds),[42] and of piperine from *Piper nigrum* – cooked and dried unripe fruit (black pepper).[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 $[C_nC_1im]^+$ 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 $[C_nC_1im][Ace]$ 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 $[C_4C_1im][Ace]$ 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 12 h to 1 h). As suggested by the authors[41] this effect seems to be related to 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-workers[40] reported a more detailed work on the kinetics, modelling and mechanism of glaucine extraction from G*lausium flavum*. In this work, the temperature dependence of the kinetics of both methanol and $[C_4C_1im][Ace]$-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 $[C_4C_1im][Ace]$ 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 $[C_4C_1im]Cl$ 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 of the 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: $[C_2C_1im]Cl$, $[C_2C_1im][C_1CO_2]$, $[C_4C_1im]Cl$, $[C_4C_1im][Tos]$, $[C_4C_1pyr]Cl$ and $[(OH)C_2C_1im]Cl$. All the studied ILs lead to a similar percentage of extracted caffeine.[42] Moreover, since $[C_4C_1im]Cl$ and $[C_4C_1pyr]Cl$ 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 authors[42] suggested that the extraction mechanism is mainly governed by the IL effect on 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 $[C_4C_1im]Cl$.[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 $[C_nC_1im]Cl$ and $[C_nC_1im][C_nCO_2]$, 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 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

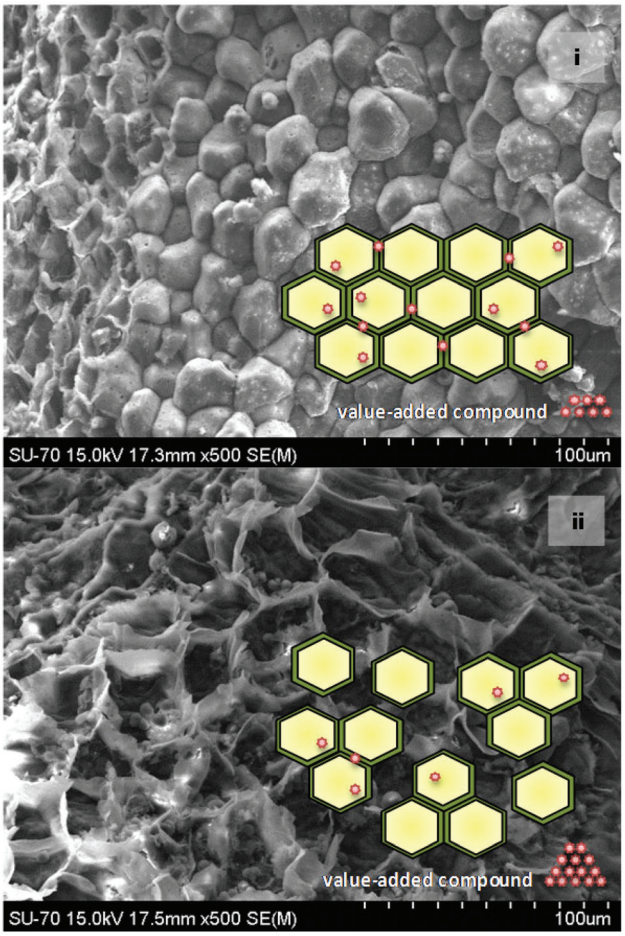


Fig. 6 SEM pictures and schematic representation of the extraction mechanism of caffeine from guaraná seeds with (i) water and (ii) an aqueous solution of $[C_4C_1im]Cl$. Adapted from Cláudio *et al.*[42] and Zirbs *et al.*[67]

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. Under the optimum conditions (time = 30 min; temperature = 70 °C; aqueous solution of $[C_4C_1im]Cl$ 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-workers[43] 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 work[43] 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 ($[N_{111(C2O(O)C12}]Cl$).[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 increased (~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 $[N_{111(C2O(O)C12}]Cl$. 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, only a slight influence through the piperine extraction was observed. 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. Ressmann *et al.*[43] also identified, by electron microscopy, an increase in 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 outmost importance.

The authors[43] 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]

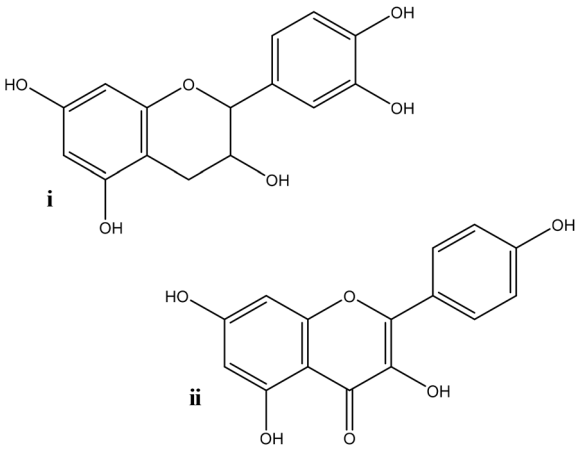


Fig. 7 Chemical structure of some flavonoids: (i) (+)-catechin; (ii) kaempferol.

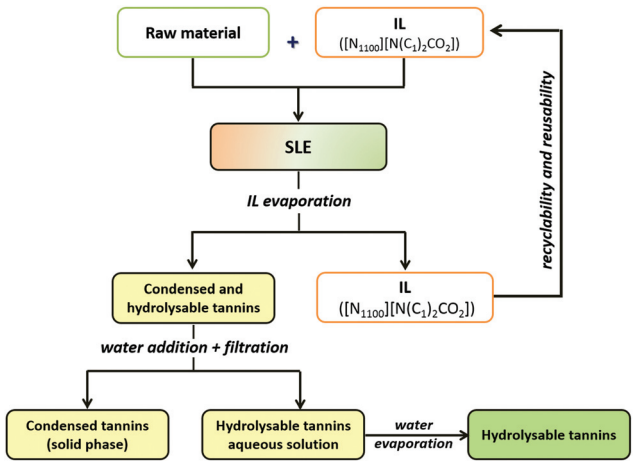


Fig. 8 Flowchart of the process used to extract vegetable tannins.[50]

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)) tanning 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]

The conventional methods applied for the extraction of hydrolysable vegetable tannins require relatively harsh conditions, such as high temperature (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 other 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

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

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

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 authors[50] 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 studies have been focused on imidazolium-based fluids, and the work published by Chowdhury *et al.*[50] represents a strong contribution to 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 in the process footprint reduction through the environment.

Rutin is present in *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 authors[52–54] found that the flavonoids extraction is anion-dependent, and which is in agreement with the results discussed before for the extraction of alkaloids. Both types of solutes (*cf.* Fig. 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 π···π and hydrogen-bonding interactions (between the target flavonoid and the IL cation) can be inferred at this stage. All authors[52–54] 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[52,53] 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] a maximum in the flavonoids extraction at 60–80 °C was observed. 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 the degradation of flavonoids was observed.[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 (≈ 0.05 mg g^{-1}), myricetin (≈ 0.04 mg g^{-1}) and quercetin (0.14 mg g^{-1}) from *Bauhinia championii* when compared with the conventional MAE and heating reflux extraction (kaempferol < 0.01 mg g^{-1}, myricetin < 0.01 mg g^{-1} and quercetin ≈ 0.06 mg g^{-1}).

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 in the time of extraction (up to 30 min) significantly improves the extraction yields. Longer times do not provide enhanced results due to a decrease in the diffusion rate. The solid–liquid ratio was finally addressed, and a maximum on the extraction yield at 30 mg L^{-1} was observed.[51] After the optimization of all the operation conditions, Wang and co-workers[51] 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.

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 studies applying pure ILs were also reported.[60–62]

With 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 authors[55] 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-workers[43] in the extraction of piperine. The extraction yield of carnosic acid increases significantly with the increase in 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 in 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]

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

Value-added compound	Natural source	Technique	IL
Carnosic acid	*Rosmarinus officinalis* (rosemary)	MAE	$[C_{10}C_1im]Br$, $[C_2C_1im]Br$, $[C_4C_1im][BF_4]$, $[C_4C_1im][NO_3]$, $[C_4C_1im]Br$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$, $[C_6C_1im]Br$, $[C_8C_1im]Br$ (water)[55]
Ginsenoside-Rg1, -Re, -Rf, -Rb1, -Rc, -Rb2, -Rb3, -Rd	Ginseng root	UAE	$[C_2C_1im]Br$, $[C_3C_1im][BF_4]$, $[C_3C_1im]Br$, $[C_3C_1im]I$, $[C_4C_1im]Br$, $[C_6C_1im]Br$ (water)[56]
Cryptotanshinone Tanshinone I Tanshinone II A	*Salvia miltiorrhiza*		$[C_{10}C_1im]Br$, $[C_{12}C_1im]Br$, $[C_{14}C_1im]Br$, $[C_{16}C_1im]Br$, $[C_8C_1im]Br$, $[C_2C_1im]Cl$, $[C_4C_1im]Cl$, $[C_6C_1im]Cl$, $[C_8C_1im]Cl$ (water)[57,58]
Astaxanthin	Shrimp waste		$[C_2C_1im][BF_4]$, $[C_4C_1im][BF_4]$, $[C_4C_1im][C_1SO_4]$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$, $[C_6C_1im][BF_4]$, $[(NH_2)C_3C_1im]Br$ (ethanol)[59]
Artemisinin	*Artemisia annua*	SLE	$[N_{11(2(O)1)0}][C_2CO_2]$, $[N_{11(2OH)0}][C_7CO_2]$ (pure IL)[60]
Limonene	Orange peels		$[C_4C_1im]Cl$, $[aC_1im]Cl$, $[C_2C_1im][C_1CO_2]$ (pure IL)[61]
Betulin	Birch bark		$[C_2C_1im][(C_1)_2PO_4]$, $[C_2C_1im][BF_4]$, $[C_2C_1im][C_2CO_2]$, $[C_2C_1im][C_3CO_2]$, $[C_2C_1im][C_{i3}CO_2]$, $[C_2C_1im][C_1CO_2]$, $[C_2C_1im][N(CN)_2]$, $[C_2C_1im][PF_6]$, $[C_2C_1im][NTf_2]$, $[C_2C_1im]Br$, $[C_2C_1im]Cl$, $[C_4C_1im]Cl$, $[C_6C_1im]Cl$, $[C_8C_1im]Cl$, $[C_{10}C_1im]Cl$, $[C_{12}C_1im]Cl$, $[C_{14}C_1im]Cl$, $[aC_1im]Cl$, $[C_1C_1im][C_3CO_2]$, $[C_1C_1im][C_1CO_2]$, $[C_4C_1pyr]Cl$, $[C_4py]Cl$, $[(OH)C_2C_1im]Cl$ (pure IL)[62]

The application of IL-based UAE was also extended to the extraction of other terpenoids, such as ginsenoside-Rg1, -Re, -Rf, -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 usual,[55] the authors investigated the effect of the IL chemical structure and some process variables.

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, $[C_3C_1im]Br$ led to an extraction yield of ≈15 mg g^{-1}. The IL concentration was also evaluated and a maximum in 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 yields obtained with $[C_3C_1im]Br$ 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^{-1}) when compared with water (≈ 13 mg g^{-1}) or ethanol (≈ 6 mg g^{-1}). Lastly, a comparison with the conventional UAE allowed us 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 tanshinones from *Salvia miltiorrhiza*.[107] Similar to the work carried out by Bica and co-workers[43] regarding the piperine extraction, Wu *et al.*[58] presented one of the most complete investigations on the use of long-alkyl chain ILs, $[C_nC_1im]Br$-based ILs (n = 8, 10, 12, 14, 16). The results obtained suggest that the extraction of tanshinones is also micelle-mediated.[58] The best extractions were acquired with the IL with the longer alkyl chain ($[C_{16}C_1im]Br$) and the extraction yields were *ca.* 0.6, 1.2 and 1.4 mg g^{-1} for cryptotanshinone, tanshinone I and tanshinone IIA, respectively.[58] The chemical structures of these terpenoids are presented in Fig. 9. The octanol–water partition coefficients of cryptotanshinone, tanshinone I and tanshinone IIA are 5.6×10^4, 2.9×10^4 and 3.7×10^5, respectively.[97] These terpenoids are very lipophilic molecules which support the results obtained. When dealing with aqueous solutions these types of compounds are better dissolved by a micelle-mediated process. On the other hand, the increase in 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: 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 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 $[C_2C_1im]Cl$ and $[C_6C_1im]Cl$, the extracted amount of tanshinones increases slightly, whereas between $[C_6C_1im]Cl$ and $[C_8C_1im]Cl$, 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 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 of ILs improves the extracted amount of tanshinone I and tanshinone II A by at least three times.[57] After the extraction of tanshinones from *Salvia miltiorrhiza* herbs, the authors[57] proposed a novel pre-concentration process through the conversion of the IL into its hydrophobic form by anion metathesis. To this aim, HPF_6 and $LiNTf_2$ were added in order to convert the $[C_8C_1im]Cl$ into the hydrophobic ILs $[C_8C_1im][PF_6]$ and $[C_8C_1im][NTf_2]$.[57] $[C_8C_1im][PF_6]$ 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]

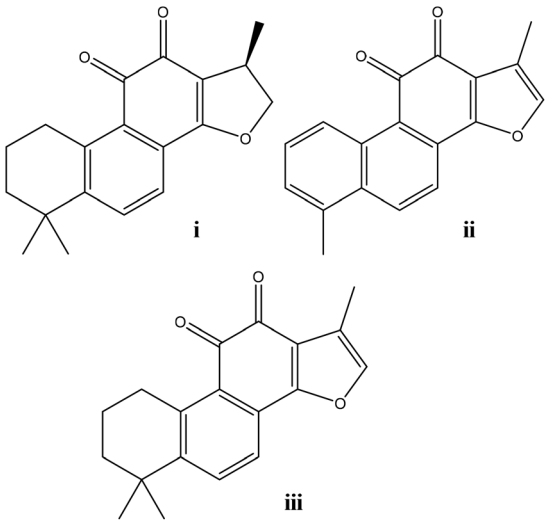


Fig. 9 Chemical structure of some terpenoids: (i) cryptotanshinone; (ii) tanshinone I; (iii) tanshinone II A.

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 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 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 and not aqueous solutions as commonly reported in the literature based on a previous choice of the optimum molecular solvent.[59] The finest results were obtained with the functionalized $[(NH_2)C_3C_1im]Br$, *ca.* 80 μg of astaxanthin per g of dried shrimp waste, due to the existence of a reductive amine group. This group protects astaxanthin against oxidation and has favourable interactions with the carotenoid functional groups. The effect of the $[(NH_2)C_3C_1im]Br$ concentration in ethanol was also analysed with the astaxanthin extraction increasing up to 0.50 M of IL.[59] A significant increase in the extraction efficiency was observed up to 60 min; after that no further improvement was observed.[59] The solid–liquid ratio of 1 : 10 was selected taking into account economic considerations.[59]

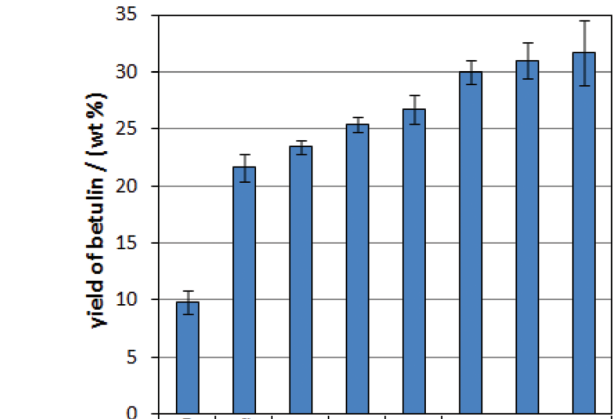
Artemisinin is a sesquiterpene lactone with pivotal importance in the malaria treatment due its very fast action against the widespread *Plasmodium falcuparum*.[110] This value-added compound is typically extracted from *Artemisia annua* using petroleum ether, heptane, hexane or toluene at high temperatures.[111] However, in 2006, Bioniqs Ltd (UK)[112] initiated a preliminary study on the possibility of using ILs as solvents in the SLE of artemisinin from *Artemisia annua*. Amongst the several ILs investigated, the biodegradable IL $[N_{11(2OH)0}][C_7CO_2]$ was identified as the best extraction solvent while presenting comparable results to those obtained by hexane at high temperatures. The optimal operational conditions were also determined: a solid–liquid ratio of 1.1 at 25 °C for 30 min.[112] Later on, in 2008, Bioniqs Ltd 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-component system). This study led to the modification of the IL from $[N_{11(2OH)0}][C_7CO_2]$ to $[N_{11(2(O)1)0}][C_2CO_2]$ with a significant improvement in the selective extraction of artemisinin.[60] Nevertheless, at this stage, Bioniqs Ltd considers that $[N_{11(2(O)1)0}][C_2CO_2]$ 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 in a Chinese patent regarding the use of an IL-based UAE process for 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-workers[61] suggested the application of 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, the ability of several ILs ($[C_4C_1im]Cl$, $[aC_1im]Cl$ and $[C_2C_1im][C_1CO_2]$) for the complete dissolution of orange peels was investigated. The complete dissolution of orange peels was observed after 3 h with $[C_2C_1im][C_1CO_2]$, while even after 24 h the ILs $[C_4C_1im]Cl$ and $[aC_1im]Cl$ provided only a partial 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 $[C_2C_1im][C_1CO_2]$ loaded with orange peel at 35 wt% led to a yield of the isolated orange oil of 4.9%.[61] Moreover, by gas chromatography–mass spectrometry (GC-MS) and nuclear magnetic resonance (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 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 to the development of a new anti-HIV drug that 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 authors[62] 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 $[(OH)C_2C_1im]Cl$) leads to comparable results to those obtained with shorter alkyl chain $[C_nC_1im]Cl$ ILs; (iii) the results obtained with $[C_4py]Cl$ 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 and 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 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. By



S/L ratio (wt %)	5	5	5	5	5	5	10	10
T (°C)	100	---	---	100	100	100	100	100
time (h)	24	24	24	24	24	24	24	15'
other		reflux	reflux					MW

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

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 authors[63] 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

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

Value-added compound	Natural source	Technique	IL
Benzofuranoids			
Senkyunolide H Senkyunolide I Z-Ligustilide	*Ligusticum chuanxiong*	MAE	$[N_{11(2(O)2OH)0}][C_2CO_2]$, $[N_{11(3N)0}][C_2CO_2]$ (pure IL)[63]
Benzopyranoids			
Aesculetin Aesculin	*Fraxinus rhynchophylla*	UAE	$[C_7H_7C_1im]Br$, $[C_7H_7C_1im]Cl$, $[C_{10}C_1im]Br$, $[C_{12}C_1im]Br$, $[C_2C_1im][BF_4]$, $[C_2C_1im]Br$, $[C_4C_1im][BF_4]$, $[C_4C_1im][ClO_4]$, $[C_4C_1im][HSO_4]$, $[C_4C_1im][Tos]$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$, $[C_4C_1im]I$, $[C_8C_1im]Br$, $[C_6C_1im]Br$, $[(HSO_3)C_4C_1im][HSO_4]$, $[(OH)C_2C_1im]Cl$ (water)[64]
Lignans			
Deoxyschizandrin Schisantherin A Schizandrin γ-Schizandrin	*Schisandra chinensis*	UAE and MAE	$[C_{10}C_1im]Br$, $[C_{12}C_1im]Br$, $[C_2C_1im]Br$, $[C_4C_1im][BF_4]$, $[C_4C_1im][C_1CO_2]$, $[C_4C_1im][ClO_4]$, $[C_4C_1im][HSO_4]$, $[C_4C_1im][NO_3]$, $[C_4C_1im][OH]$, $[C_4C_1im]Br$, $[C_6C_1im]Br$, $[C_8C_1im]Br$ (water)[65,66]
Phenolic acids			
Ellagic acid	*Acacia catechu* (catechu) and *Terminalia chebula* (myrobolan)	SLE	$[N_{1100}][N(C_1)_2CO_2]$ (pure IL)[50]
Ellagic acid Gallic acid	*Psidium guajava* and *Smilax china*	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]
Rosmarinic acid	*Rosmarinus officinalis* (rosemary)		$[C_{10}C_1im]Br$, $[C_2C_1im]Br$, $[C_4C_1im][BF_4]$, $[C_4C_1im][NO_3]$, $[C_4C_1im]Br$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$, $[C_6C_1im]Br$, $[C_8C_1im]Br$ (water)[55]

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, $[C_4C_1im]Br$ 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^{-1} 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 of 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, deoxyschizandrin and γ-schizandrin. All these lignans display anti-hepatotoxic, antioxidant and anti-inflammatory characteristics.

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 $[C_4C_1im]$-based ILs, the $[C_4C_1im]Br$ 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

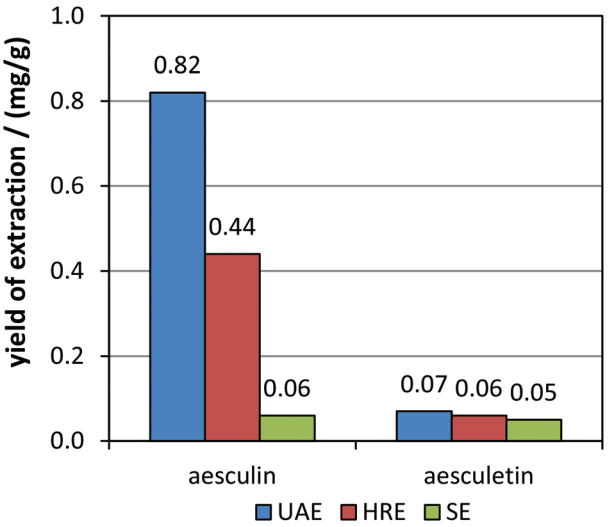


Fig. 11 Yield of extraction of aesculin and aesculetin by three extraction methods/solvents.[64] HRE – heating reflux extraction; SE – stirring extraction.

($[C_nC_1im]^+$ with n = 2–12) and $[C_{12}C_1im]Br$ 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 $[C_{12}C_1im]$-based ILs led to the best extraction efficiencies with a total yield of lignans of ≈99 and >200 mg kg^{-1}, respectively.[65] Thus, the IL $[C_{12}C_1im]Br$ 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 in 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 in the solid–liquid ratio until 1 : 12 significantly increases the extraction yield.[65] Finally, and comparing with conventional hydrodistillation, 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 acids, 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 carnosic acid and essential oils from rosemary by IL-based MAE. All these works[50,53,55] were described above.

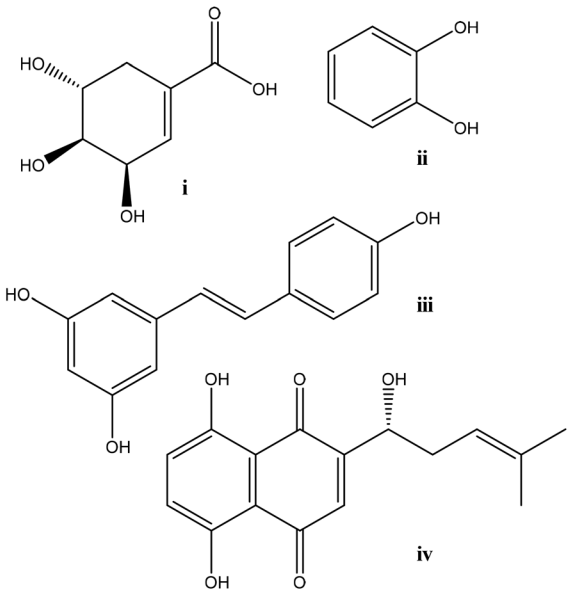


Fig. 12 Chemical structure of aromatic natural compounds: (i) shikimic acid; (ii) pyrocatechol; (iii) *trans*-resveratrol; (iv) shikonin.

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 IL solutions as extraction solvents, are described in Table 6. Ethanol and water were used as molecular solvents, three separation techniques were applied, namely SLE, MAE and UAE, as well as 10 ILs, mainly $[C_nC_1im]$-based fluids.

Pyrocatechol is a simple aromatic compound which was already extracted from *Acacia catechu* and *Terminalia chebula*

Table 6 List of aromatic compounds extracted from natural sources using ILs or IL solutions (the molecular solvent is presented between parentheses) and different extraction techniques employed

Value-added compound	Natural source	Technique	IL
Shikimic acid	*Illicium verum* (star anise)	MAE	$[C_2C_1im][BF_4]$, $[C_2C_1im][CF_3SO_3]$, $[C_2C_1im][C_1CO_2]$, $[C_2C_1im][NTf_2]$, $[C_2C_1im][PF_6]$, $[C_2C_1im]Cl$ (pure IL)[67]
		SLE	$[C_2im][HSO_4]$, $[C_2C_1im][HSO_4]$, $[(HSO_3)C_4C_1im][H_2PO_4]$, $[(HSO_3)C_4C_1im][HSO_4]$, $[(HSO_3)C_4C_1im][NTf_2]$, $[(HSO_3)C_4C_1im]Br$, $[(HSO_3)C_4C_1im]Cl$ (ethanol)[68]
	Ginkgo biloba		$[C_4C_1im]Cl$ (pure IL)[69]
Pyrocatechol	*Acacia catechu* (catechu) and *Terminalia chebula* (myrobolan)		$[N_{1100}][N(C_1)_2CO_2]$ (pure IL)[50]
Pyrocatechol Trans-resveratrol	*Psidium guajava* and *Smilax china*	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]
Trans-resveratrol	*Rhizma polygoni*		$[C_4C_1im][BF_4]$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$ (water)[39]
Shikonin β,β′-dimethylacrylshikonin	*Arnebia euchroma*	UAE	$[C_2C_1im][BF_4]$, $[C_4C_1im][BF_4]$, $[C_6C_1im][BF_4]$, $[C_6C_1im][PF_6]$, $[C_8C_1im][BF_4]$, $[C_8C_1im][PF_6]$ (pure IL)[70]

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 (+)-chatechin and quercetin.[48,53]

In 2007, Li and co-workers[39] 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 ($[C_4C_1im][BF_4]$, $[C_4C_1im]Br$ and $[C_4C_1im]Cl$) in addition to the operational conditions which were optimized by an orthogonal design L_9 (3^4) approach.[39] The best results were obtained with $[C_4C_1im]Br$ in contrast with $[C_4C_1im][BF_4]$ which was shown 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, a 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% *trans*-resveratrol extraction yield was attained under the optimum conditions.[39]

Shikimic acid is the starting material for the production of the neuraminidase inhibitor Tamiflu™ (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 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 of 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 Brönsted acidic IL solutions, both as solvents and catalysts, envisaging the synthesis of shikimic acid ethyl ester and the ketal ester (*in situ*). The authors[68] investigated the conversion of shikimic acid into ethyl ester in ethanol solutions of $[(HSO_3)C_4C_1im][HSO_4]$, $[(HSO_3)C_4C_1im][NTf_2]$, $[(HSO_3)C_4C_1im]Br$ and $[(HSO_3)C_4C_1im]Cl$. High conversions into ethyl ester (81 to 99%) were observed, albeit the complete conversion was only attained with $[(HSO_3)C_4C_1im][NTf_2]$. 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 $[(HSO_3)C_4C_1im][HSO_4]$ + ethanol solutions.[68] An extraction yield of 12.7% was obtained when a mass-equivalent amount of $[(HSO_3)C_4C_1im][HSO_4]$ was used.[68] Additional parameters were also evaluated. As observed in most studies, the increase of the IL concentration leads to an increase in 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 $[(HSO_3)C_4C_1im][HSO_4]$ or $[(HSO_3)C_4C_1im][NTf_2]$. 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 of the IL–solute interactions.[67] Bica and co-workers[67] focused on $[C_2C_1im]$-based ILs that presented different abilities for the cellulose processing and biomass dissolution (*cf.* Table 6). $[C_2C_1im][C_1CO_2]$ 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] $[C_2C_1im][C_1CO_2]$ led to the best results (10.7 wt%) followed by other hydrophilic ILs, namely $[C_2C_1im][CF_3SO_3]$ (10.3 wt%) and $[C_2C_1im]Cl$ (10.0 wt%). On the other hand, the hydrophobic ILs presented the poorest results and in the case of $[C_2C_1im][PF_6]$ 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 a high temperature (100 °C) and further production of hydrofluoric acid.[84]

Transmission electron microscopy (TEM) was also applied to infer on the biomass morphology after dissolution in the IL.[67] $[C_2C_1im][C_1CO_2]$ almost completely dissolved the star anise and destroyed its original structure, while $[C_2C_1im][PF_6]$ 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 $[C_4C_1im]Cl$ was selected as the extraction solvent and the obtained results, at different temperatures (100, 130 and 150 °C), were 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 antivirus 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 $[C_nC_1im][BF_4]$ ILs revealed that as n increases, the

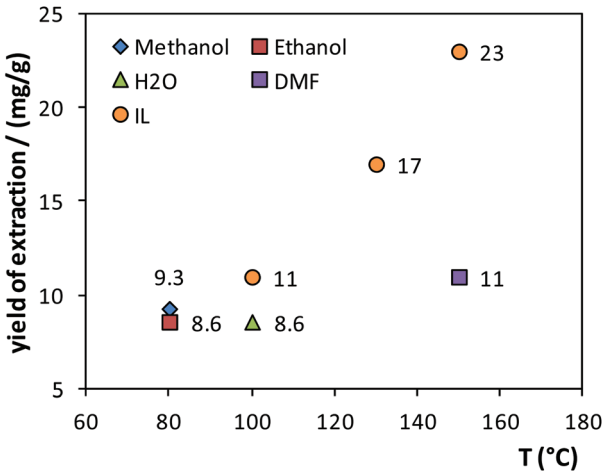


Fig. 13 Yield of shikimic acid extraction from *Ginkgo biloba* using different extraction methods at distinct temperatures.[69]

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^{-1} 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 studies 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 IL solutions as solvents are listed in Table 7.

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 forsythiae*. The studies 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 $[C_6C_1im][PF_6]$ 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]

Table 7 List of mixtures of value-added compounds extracted from natural sources using ILs or IL solutions (the molecular solvent is presented between parentheses) and different extraction techniques employed

Value-added compound	Natural source	Technique	IL
Essential oils	*Dryopteris fragrans* and *Fructus forsythiae*	MAE	$[aC_1im]Cl$, $[C_2C_1im][C_1CO_2]$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$ (pure IL)[71,72]
	Illicium verum and *Cuminum cyminum*		$[C_6C_1im][PF_6]$ (pure IL)[73]
	Rosmarinus officinalis (rosemary)		$[C_{10}C_1im]Br$, $[C_2C_1im]Br$, $[C_4C_1im][BF_4]$, $[C_4C_1im][NO_3]$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$, $[C_6C_1im]Br$, $[C_8C_1im]Br$ (water)[55]
	Schisandra chinensis		$[C_{10}C_1im]Br$, $[C_{12}C_1im]Br$, $[C_2C_1im]Br$, $[C_4C_1im][BF_4]$, $[C_4C_1im][C_1CO_2]$, $[C_4C_1im][ClO_4]$, $[C_4C_1im][HSO_4]$, $[C_4C_1im][NO_3]$, $[C_4C_1im][OH]$, $[C_4C_1im]Br$, $[C_4C_1im]Cl$, $[C_6C_1im]Br$, $[C_8C_1im]Br$ (water)[65]
Gallotannins	*Galla chinensis*	UMAE	$[C_4C_1im][BF_4]$, $[C_4C_1im]Cl$, $[C_4C_1im]Br$ (water)[74]
Suberin	*Quercus suber* (cork)	SLE	$[C_2C_1im][C_2OCO_2]$, $[C_2C_1im][C_1CO_2]$, $[C_2C_1im]Cl$, $[C_4C_1im]Cl$, $[N_{111(2OH)}][C_3CO_2]$, $[N_{111(2OH)}][C_5CO_2]$, $[N_{111(2OH)}][C_{i3}CO_2]$, $[N_{111(2OH)}][C_1CO_2]$, $[N_{111(2OH)}][C_2OCO_2]$,[75] $[C_2C_1im][C_5CO_2]$, $[N_{111(2OH)}][C_5CO_2]$, $[N_{111(2OH)}][C_7CO_2]$, $[N_{111(2OH)}][C_9CO_2]$ (pure IL)[76]
Saponins Polyphenols	*Ilex paraguariensis* (mate) and *Camellia sinensis* (tea)		$[aC_1im]Cl$, $[C_2C_1im][C_2OCO_2]$, $[C_2C_1im][CF_3SO_3]$, $[C_2C_1im][C_2SO_4]$, $[C_2C_1im][C_1CO_2]$, $[C_2C_1im][N(CN)_2]$, $[C_2C_1im]Cl$, $[C_4C_1im]Cl$, $[C_6C_1im]Cl$, $[C_7H_7C_1im]Cl$, $[C_8C_1im]Cl$, $[N_{111(2OH)}][NTf_2]$, $[N_{111(2OH)}]Cl$, $[(OH)C_2C_1im]Cl$ (water)[77]
Para Red Sudan (I, II, III and IV)	Chilli powder and chilli oil		$[C_4C_1im][PF_6]$, $[C_6C_1im][PF_6]$ (pure ILs)[78]

Jiao *et al.*[71,72] studied the application of several ILs – [aC$_1$im]Cl, [C$_2$C$_1$im][C$_1$CO$_2$], [C$_4$C$_1$im]Br and [C$_4$C$_1$im]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 [C$_2$C$_1$im][C$_1$CO$_2$] is the best candidate.[71,72] Other operational parameters were optimized by central composite design and a first order kinetic model.[71,72] Under the optimum conditions (irradiation power of 300 W, pre-treatment temperature of 76 °C, [C$_2$C$_1$im][C$_1$CO$_2$] 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, [C$_2$C$_1$im][C$_1$CO$_2$] at 77 wt% and pre-treatment time of 4.3 min for *Fructus forsythiae*) a significant increase in 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]

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 studies,[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 authors[74] studied the substitution of organic solvents in UMAE with the following ILs: [C$_4$C$_1$im][BF$_4$], [C$_4$C$_1$im]Br and [C$_4$C$_1$im]Cl. The optimum UMAE conditions found are as follows: 2.5 mol L^{-1} of [C$_4$C$_1$im]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 obtained 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 ultrasound during the extraction process intensifies the mass transfer and the biomass cell disruption which allow 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.

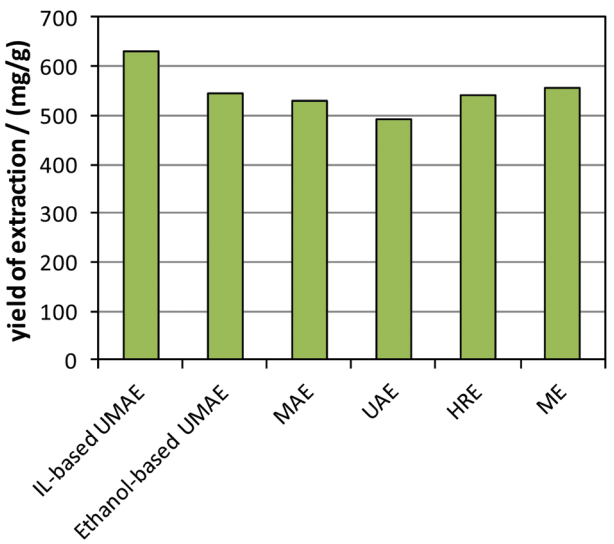


Fig. 14 Yield of gallotannins extraction from *Galla chinensis* with different extraction techniques.[74] HRE – heating reflux extraction; ME – maceration extraction.

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 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 7) 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 [C$_2$C$_1$im]Cl and [C$_4$C$_1$im]Cl were not able to dissolve significant amounts of refined cork.[75] However, when the Cl$^-$ anion was substituted by [C$_2$OCO$_2$]$^-$ or [C$_1$CO$_2$]$^-$, 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$_n$CO$_2$]$^-$, led also to a favourable effect on the dissolution of suberin – due to an increase in 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 [C$_5$CO$_2$]$^-$ anion was also confirmed by ^{1}H NMR spectroscopy. Consequently, the biocompatible and biodegradable nature of [N$_{111(2OH)}$][C$_5$CO$_2$] 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: [C$_2$C$_1$im][C$_5$CO$_2$] (30%) < [N$_{111(2OH)}$][C$_9$CO$_2$] (59%) < [N$_{111(2OH)}$][C$_7$CO$_2$] (64%) < [N$_{111(2OH)}$][C$_5$CO$_2$] (67%).[76] The different extraction efficiencies obtained with the ILs [C$_2$C$_1$im][C$_5$CO$_2$] and [N$_{111(2OH)}$][C$_5$CO$_2$] undoubtedly confirm the cholinium cation role in 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. Poly-

phenols 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 $[C_7H_7C_1im]Cl$ 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 in 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 $[C_2C_1im]Cl$ and $[N_{111(2OH)}]Cl$ led to the highest extraction yields while the $[C_7H_7C_1im]Cl$ 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 a solvent for the extraction of saponins and phenolic compounds, either from mate or tea. In addition 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 non-toxic, 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, high-performance liquid chromatography (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 ($[C_4C_1im][PF_6]$ and $[C_8C_1im][PF_6]$) and the IL volume and extraction time effects were also established.[78] The higher extraction efficiencies were attained with pure $[C_8C_1im][PF_6]$ 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 3.2×10^5 and 5.0×10^8.[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 $[C_8C_1im][PF_6]$ 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 chilli oil matrix and where the extraction recoveries were similar.[78] Finally, the authors applied the proposed method to real food samples – chilli powder, chilli oil and food additives. The recoveries obtained varied between 77–110% in chilli powder, 71–108% in chilli oils and 71–107% in food additives.[78]

Lipids extraction from microalgae

In the last few decades, due to a fast increase in energy consumption, with the decrease and unstable supply of petroleum and the global warming intensification, we have been facing an amplified interest in 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 does not allow the exploitation of agricultural products on 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 5 articles were published[79–83] 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 IL solutions used as solvents in the lipids extraction are listed in Table 8.

Young *et al.*[79] reported the good performance of $[C_2C_1im][C_1SO_4]$-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 favourable for the target extraction.[80] $[C_4C_1im][CF_3SO_3]$,

Table 8 List of aquatic biomass sources, ILs or IL solutions (the molecular solvent is presented between parentheses) used and different extraction techniques employed in lipids extraction

Natural source	Technique	IL
Chlorella vulgaris	SLE	$[C_2C_1im][C_1SO_4]$ (methanol)[79]
		$[C_4C_1im][CF_3SO_3]$, $[C_4C_1im][C_1SO_4]$, $[C_4C_1im][C_1SO_3]$, $[C_4C_1im][BF_4]$, $[C_4C_1im][PF_6]$, $[C_4C_1im][NTf_2]$, $[C_4C_1im]Cl$, $[C_2C_1im][C_1SO_4]$, $[C_2C_1im]Cl$, $[C_2C_1im]Br$, $[C_2C_1im][C_1CO_2]$ (methanol)[80]
		$[C_2C_1im][C_1CO_2]$, $[C_2C_1im][HSO_4]$, $[C_2C_1im][(C_2)_2PO_4]$, $[C_2C_1im][SCN]$, $[C_2C_1im][NTf_2]$ (pure IL or salt mixtures)[81]
	UAE	$[C_4C_1im][C_1SO_4]$ (pure IL)[82]
Sargassum fulvellum, Laminaria japonica and *Undaria pinnatifida*	SLE	$[C_4C_1im]Cl$ (mineral acids)[83]

$[C_4C_1im][C_1SO_4]$ and $[C_2C_1im][C_1SO_4]$ presented the best extraction results (125.4, 118.4 and 118.8 mg g^{-1} of dried weight, respectively) compared with the commonly applied method of Bligh and Dyer (106.2 mg g^{-1} of dried weight).[80] On the other hand, Malihan *et al.*[83] placed more emphasis on sugar 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 $[C_4C_1im]Cl$, and where the combination $[C_4C_1im]Cl$/HCl dictated the higher extraction performance observed for carbohydrates.[83]

Recently, Kim *et al.*[82] suggested a new method for the extraction of lipids 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 Bligh and Dyer's method, respectively; (ii) 47 mg g^{-1} were attained when $[C_4C_1im][C_1SO_4]$ was used; and (iii) the amount of lipids extracted using $[C_4C_1im][C_1SO_4]$ was 1.6 times higher than that using UAE (75 mg g^{-1}).[82] Moreover, the IL-based UAE process drastically decreases the time of extraction.[82]

At 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 authors[81] observed that these mixtures display a better performance than their singular compounds due to synergetic effects. The mixture composed of $FeCl_3{\cdot}6H_2O$ and $[C_2C_1im][C_1CO_2]$ led to an extraction yield of lipids of 227.6 mg g^{-1} (compared against the 113.0 and 218.7 mg g^{-1} obtained with the pure compounds).[81] Moreover, under the optimum conditions identified by the authors ($FeCl_3{\cdot}6H_2O$/$[C_2C_1im][C_1CO_2]$ ratio of 5 : 1, 90 °C and 1 h of extraction time) the fatty acid content of the extracted lipids was 981.7 mg g^{-1}, 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 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.

Table 9 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]	✓
Flavonoids	IL distillation[50]	✓
	High-speed counter-current chromatography[51]	✓
Terpenoids	Solid-phase extraction[59]	✓
	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]	✓
	Macroporous resin[74,135]	✓
Others	IL distillation[50]	✓
	Back-extraction with organic solvents[63]	✓

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 9 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 of 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[74,135] 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 favourable 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-workers.[61] After distillation and condensation, essential oils can be easily

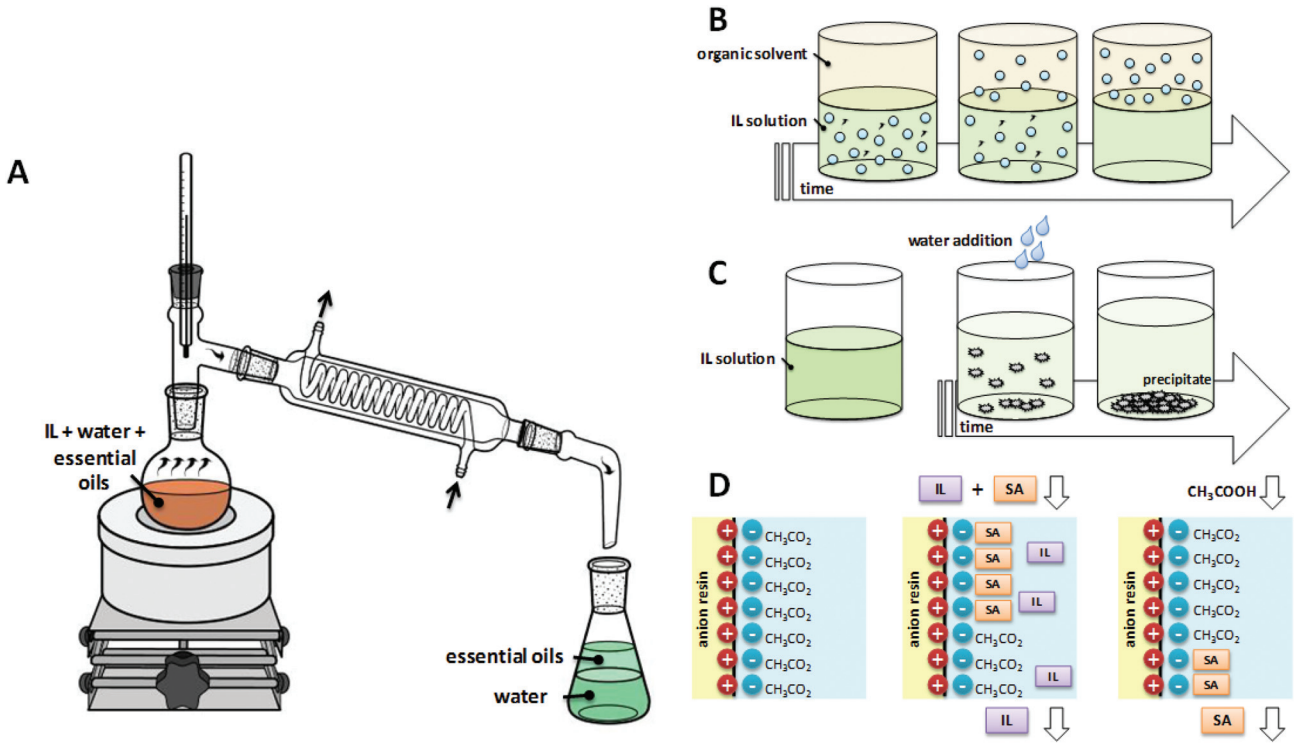


Fig. 15 Schematic representation of the methods proposed for the isolation of value-added compounds after the extraction with ILs or IL solutions. A – hydro-distillation; B – back-extraction; C – precipitation with water; D – anion exchage resin (adapted from Zirbs *et al.*[67]).

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.

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 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 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 hand, and although not applied on any of the studies reviewed in this manuscript, supercritical CO_2 can be foreseen as a potential alternative to the back-extraction and precipitation steps as suggested in the literature.[136,137] Supercritical CO_2 is amongst the "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. 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.*[74,135] 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.*[74,135] 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 authors[51] 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 authors[51] did not 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 does not 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 lipid recovery, no particular process was suggested since these compounds are not soluble in the extraction solvents, resulting in 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 advancement 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 vital issues both to support the economic viability and to minimize the environmental footprint of the proposed processes.

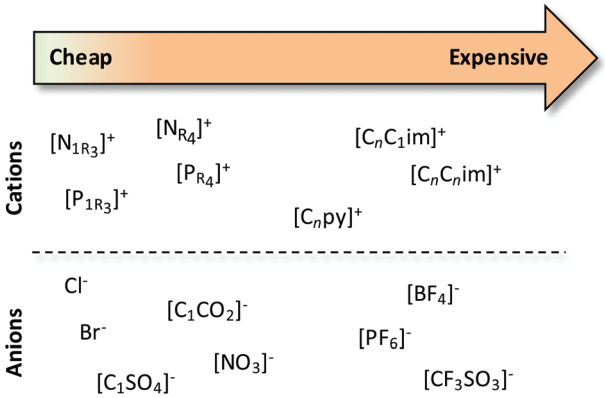


Fig. 16 Schematic illustration of the relative prices of ILs estimated based on the cost of the starting materials used in their synthesis.[140]

Table 10 Industrial production price of some organic solvents and ILs[143–147]

Organic solvents per $US		Ionic liquids per $US	
Toluene	0.74–1.05 L^{-1}	$[C_nC_1im]$-based	14–34 kg^{-1}
Ethanol	0.82–0.98 L^{-1}	$[C_1im][HSO_4]$	2.96–5.88 kg^{-1}
Methanol	0.25–0.54 L^{-1}	$[N_{2220}][HSO_4]^a$	1.24 kg^{-1}
Acetonitrile	1.06–1.12 kg^{-1}	$[N_{111(2OH)}]Cl$	1.21 kg^{-1}
n-Butyl acetate	1.48–1.59 kg^{-1}	$[N_{(10)(10)11}]Cl^a$	8.71 kg^{-1}
Chloroform	0.53–1.04 kg^{-1}	$[N_{11(13)(C7H7)}]Cl^a$	5.28 kg^{-1}
Ethylene glycols	1.43 kg^{-1}	$[N_{1(2OH)(TH)(TH)}][C_1SO_4]^a$	2.27 kg^{-1}
n-Methyl pyrrolidone	4.08–4.19 kg^{-1}		
Sulfolane	~3.7 kg^{-1}		

[a] $[N_{2220}][HSO_4]$ – triethylammonium hydrogensulphate; $[N_{(10)(10)11}]Cl$ – didecyldimethylammonium chloride; $[N_{11(13)(C7H7)}]Cl$ – cocoalkonium chloride; $[N_{1(2OH)(TH)(TH)}][C_1SO_4]$ – dihydrogenated tallowoylethyl hydroxyethylmonium methylsulphate.

The high production costs associated with ILs recurrently create a large controversy on the viability of their application on 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 10. 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 solvent application should also cover the costs associated with, 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 studies 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 (organic solvents with 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 in the extraction yield, the reduction in the extraction time and the possibility of significantly reducing the environmental impact of the process, are excellent reasons to make 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 studies, 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-workers[42] 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 have 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

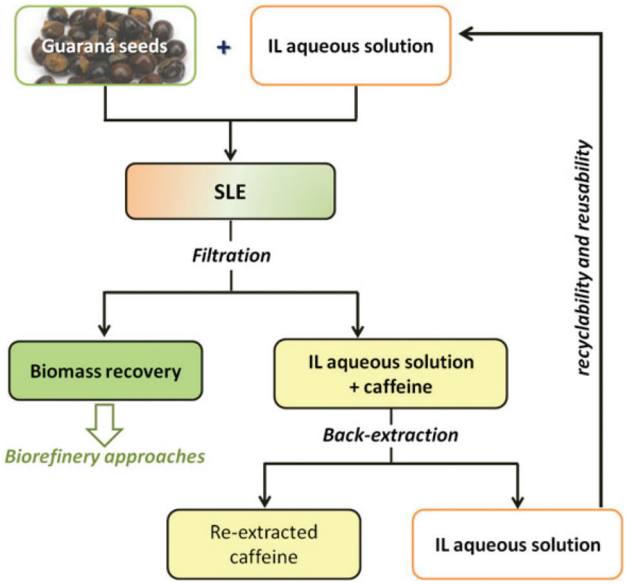


Fig. 17 Flowchart of the process used to extract caffeine from guaraná seeds.[42]

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 with the extraction of a particular value-added compound when ILs are used as extraction solvents. In eqn (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 with 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 eqn (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}^{-1}, an IL price of 20\$ L^{-1} 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 factor responsible for the product price. Small concentrations (of the order of 1 wt%) represent small slopes which means that, for an input of for instance of 1\$ kg_{biom}^{-1} in the return, the price of the value added-compound needs to increase 100\$ kg_{prod}^{-1}.

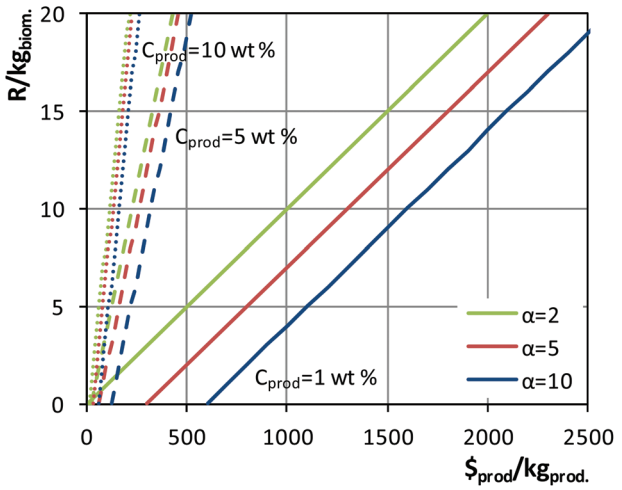


Fig. 18 Return obtained for each kg of treated biomass as a function of the value-added compounds cost.

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 it 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.

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, π···π, 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 from hydrolysis and form hydrofluoric acid. This reaction leads to adverse effects either in the degradation of the target biomolecule or in the IL irreversible loss. Even thus, [C$_n$C$_1$im][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 of 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 of the product recovery and of the solvent 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 the 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.

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