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Emerging application of extraction phase of ionic and non-ionic deep eutectic solvents toward natural herbal medicine

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ABSTRACT

The concept of sustainable development has affected the perception, process, and methods of extraction process. In that sense, replacing traditional organic solvents with eco-friendly solvents is of utmost importance. The extraction and separation of bioactive compounds from natural herbal medicine using DESs has attracted significant interest in industry and academia. This review summarizes the efforts dedicated to the applying ionic and non-ionic DESs to extract bioactive compounds from natural herbal medicine over the last five years. It also demonstrated the differences in the extraction ability of ionic and non-ionic DESs for different types of active components from natural herbal medicine. The toxicity of DESs is summarized to determine the sustainable of DESs as green solvents. Furthermore, this review presents some critical analysis to determine if using DESs as extraction solvents is sufficient for greening an extraction methodology.

1. Introduction

Diverse approaches to extracting and separating bioactive compounds have exploded in popularity because of the rising demands of the pharmaceutical industry. Bioactive compounds originated from natural herbal medicine normally come from secondary metabolites, which are essential for several vital mechanisms [1]. The bioactive compounds obtained from natural herbal medicine can be categorized as flavonoids, isoprenoids, phenolic acid, alkaloids [2]. To the best of the authors' knowledge, components from natural herbal medicine accounts for 60% of all approved anti-cancer drugs [3–5]. Most of these components are used widely in the healthcare industry to manufacture agricultural chemicals, nutrients, and cosmetics [1,6].

Traditional extraction methodologies such as maceration, percolation, Soxhlet extraction, and solvent extraction have been slowly replaced with modern extraction techniques, because of the complicated extraction periods, high cost, low yield, and other factors. Currently, alternative extraction methods with a lower impact on environmental protection are attempting to replace traditional extraction methods. The most likely method is to use a type of green solvents to replace the commonly used hazardous solvents used widely in industry [7–11].

Deep eutectic solvents (DESs), introduced by Abbott et al. in 2003 [12], have emerged as promising and green solvents to develop environmentally friendly solvents [13]. DESs as eutectic mixtures consist of a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD) that can maintain eutectic liquid and

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solid-liquid mixed state at room temperature [14,15]. The unique liquid state at room temperature meets the basic demand for a solvent in extraction and separation. In recent decades, their remarkable ability to dissolve various bioactive compounds from natural herbal medicine matrices has piqued the interest of the scientific community [16–20]. As a designable task-specific solvents, DESs are commonly used for the extraction and separation of bioactive compounds from herbal medicines, overcoming the limitations of traditional extraction methods through the use of more effective extraction methods.

In this review, a new classification method is used to distinguish different types of DESs. Currently, with the rapid increase in the number of DESs, various types of HBA are being used to synthesize DESs. However, in the early stages of DESs development, compounds with ionic forms such as quaternary ammonium salts or metal halides were used as the only HBA. However, with the leapfrog development of DESs types, more and more non-ionic compounds are commonly used as HBA in the synthesis of new DESs. Therefore, it is necessary to use a classification method to distinguish this type of DESs to better distinguish the differences between ionic and non-ionic DESs during the extraction process. This is a new perspective to distinguish the application prospect of DESs in the field of extraction and separation from ionic and non-ionic aspects [21–23]. The ionic and non-ionic states of DESs are defined by whether the HBA and HBD in the DESs contain ionic components. The classical DESs, choline chloride (ChCl)/urea (1:2) can be considered an ionic DESs because of the presence of ionic HBA. ChCl is the most widely used HBA in preparation of ionic DESs. Furthermore, some inorganic/organic salts, such as quaternary ammonium salts, quaternary phosphate salts, $ZnCl_2$ and $FeCl_3$, are also ionic and can form ionic DESs. Ionic DESs, such as ChCl-based DESs, are similar to ionic liquids (ILs) because of the presence of anions and cations. On the other hand, DESs provide another liquid form completely different from ILs, i.e., non-ionic DESs. For example, menthol/thymol (1:1) can be defined as a non-ionic DESs mainly because its eutectic system does not contain ionic components. Non-ionic DESs have been developed by combining primary metabolites and bio-renewable starting materials, such as sugars, alcohols, amino acids, organic acids, and terpenoids [24,25]. As a green solvent, DESs, whether ionic or non-ionic, are widely recognized by the academic community [26]. The cytotoxicity of ionic DESs has received extensive attention recently because of their similar composition to ILs [27–31]. The cytotoxicity of ionic DESs is significantly affected by the HBD components [11,32]. Non-ionic DESs, however, fully represent green chemistry principles because of the natural components. They are considered the third solvents in living cells, which explains their high solubility of bioactive compounds from natural herbal medicine matrices.

Methods of extracting and separating bioactive ingredients from natural plant matrixes more effectively in an eco-friendly way have attracted considerable attention. Plants are important resources for medicines and food. Many secondary metabolites from plants can have pharmacological or toxicological effects on humans and animals, including terpenoids, alkaloids, phenolic compounds, and flavonoids [33]. In 2018, compared with using traditional solvents, a two-phase DESs system showed more extraordinary extractability with advantages of waste reduction, environment friendly and efficiency as shown in Fig. 1 [34]. Considering safety, efficiency, and sustainable development, DESs have been applied to extract, isolate, and purify bioactive compounds from plants.

Generally speaking, the extraction of active components from herbal drugs is not only influenced by extraction technology, temperature, solvent/liquid ratio, but also by the physical and chemical properties of the DESs used. At present, the component structure of DESs has been proven to be crucial in the extraction process, as it determines characteristics such as polarity, physicochemical interactions, solubility, and viscosity. Among them, viscosity is a crucial factor, so water, as the third component, is often used to reduce the overall viscosity of DESs. For example, in the combination of organic acids (lactic acid) and two carbohydrate sugars (fructose and glucose) with choline chloride, without the addition of water, it is impossible to have the initial synthesis of DESs based on sugars (fructose and glucose). Therefore, moisture as the third component can effectively avoid this situation. In 2020, Razborsek et al. reported a type of DESs based on water as the third component [35]. All solvents prepared in this system were proven to be stable, transparent, and high viscosity liquids, and no precipitates were formed during the preparation, extraction, and analysis processes. As others have observed, due to the large amount of excess water breaking the hydrogen bonds between DESs components and losing the eutectic properties of the resulting solvents, the author did not excessively increase the molar ratio of water in this type of DESs system in pursuit of lower viscosity. In 2019, Gómez et al. reported a non-ionic DESs based on water components for extracting soluble polysaccharides from banana peel [36]. In this system, a new viewpoint was proposed regarding the role of water components in the DESs system, which is to change the conductivity and water activity of the DESs system by changing the water ratio. Utilizing moisture to reduce the hydrogen bonding forces between components, thereby providing more hydrogen bonding interactions for identifying target substances. Takla et al. also reported the same conclusion, stating that adding water as a component of DESs can effectively improve the extraction efficiency of alkaloids [37]. This system dilutes the hydrogen bonding between components through water and also confirms that when the water ratio exceeds a certain limit, it will lead to the loss of existing hydrogen bonds. Therefore, the unique structure of DESs disappears as the polarity of the mixture increases.

The primary goal of this review is to summarize the findings obtained over the last five years by combining ionic and non-ionic DESs with novel extraction methods for the extraction of bioactive components from natural herbal medicine matrices. The recovery and toxicity of the extracted analytes and DESs are also discussed. The majority of these papers are mentioned and presented in the corresponding tables systematically.

2. Deep eutectic solvents: formation and characteristics

2.1. Physicochemical properties of ionic and non-ionic DESs

The physicochemical properties of ionic and non-ionic DESs, such as melting point, density, conductivity, surface tension, polarity, and viscosity, have attracted considerable interest owing to their low toxicity, high biocompatibility and biodegradability on extraction [38,39].

Density is one of the fundamental parameters for extraction in liquids. Most hydrophilic ionic DESs reported have higher densities than water (>1 g/cm^3) [40]. By contrast, some hydrophobic ionic DESs have densities comparable to or lower than water [41]. Density is influenced by many factors, including temperature, water content in the DESs composition, the nature of the HBAs and HBDs, and the molar ratio of HBD/HBA [40]. The relationship between the water content and density of ChCl-lactic acid-based DESs (1:2) was investigated showing that an increase in water content leads to a linear decrease in density [42].

In general, the melting point of ionic and non-ionic DESs is lower than that of its constituents. In the formation process of DESs, the current mainstream theory believes that the proportion of hydrogen bond donors of DESs determines their melting point. This is supported mainly by the fact that an increase in hydrogen bond

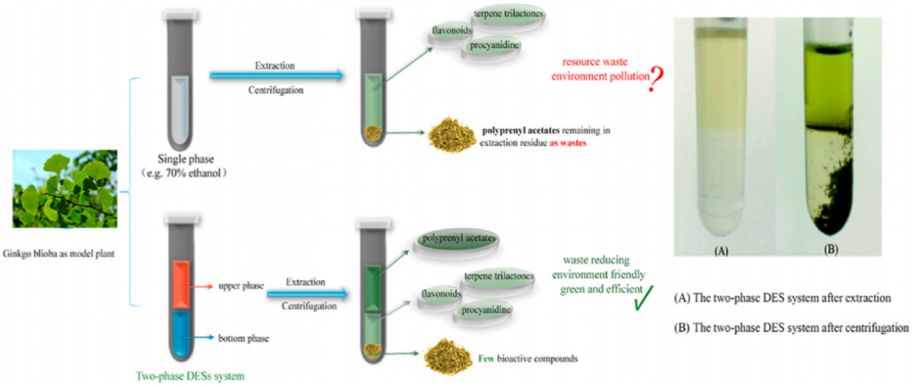

Fig. 1. Schematic procedure of using a two-phase DESs system to extract bioactives from *Ginkgo biloba* leaves (Reproduced with permission from Ref. [34]).

interaction of anionic groups leads to a decrease in the interaction with cationic groups. In this process, the lattice energy decreases because of the weak interaction force, lowering the melting point [38]. The same decrease in melting point was observed in HFIP-based ionic DESs, which could be attributed to the hydrogen-bond interactions between HFIP and quaternary ammonium salts disrupting the crystalline structure of the quaternary ammonium compounds [43].

Viscosity is a vital property of DESs. Most ionic DESs showed relatively high viscosity at room temperature(>100 mPa s) owing to extensive hydrogen bond interactions, resulting in reduced mass transfer and poor target compound extraction yields [39,41,44]. In the literature, increasing temperature reduced the viscosity, for example, from 20 °C to 80 °C, an approximately 90% reduction in viscosity was observed for ChCl-lactic acid-based DESs (1:2), with water contents ranging from 0 to 35%. On the other hand, temperatures above a certain threshold are unfavorable for target compound extraction, but viscosities below a certain threshold are also unfavorable for extraction. The viscosity is inversely proportional to the water content at a specific temperature [42,45]. At the same time, the viscosity of the DESs system is influenced by the composition of the DESs. For example, a ChCl system containing malic acid shows higher viscosity than one with citric acid [46].

Most ionic DESs have relatively high viscosity, which controls conductivity as a major factor. Hence, these solvents have poor ionic conductivity at room temperature. Therefore, the parameters affecting the viscosity, including temperature, HBA/HBD, and water content, also influence the conductivity [39].

Surface tension closely correlates with viscosity; highly viscous liquids have high surface tensions [39]. Surface tension decreases as the temperature rises, according to a linear correlation with temperature similar to the viscosity trend [38].

Generally, the surface tension of DESs is higher than that of most conventional solvents [38]. As an important property of solvents, the polarity of DESs is influenced by their composition and temperatures [47]. DESs composed of organic acids are more acidic than those composed of sugar or polyalcohol; consequently, they are more polar [48]. The polarity of DESs may influence their ability to extract, as evidenced by a ChCl-glycerol-based DESs with increasing polarity and a good ability to contribute and accept hydrogen through the natural product matrix [49].

Unlike ionic DESs, most non-ionic DESs examine the melting temperature of specific stoichiometric mixtures of substances but do not investigate their phase behavior [26]. On the other hand, the reason for the melting point depression is unclear. The freezing points of long-chain alkanol and alkyl carboxylic acid-based DESs at the eutectic ratio are lower than that of their components, significantly reducing and then ramping up as the molar concentration of HBA (alkanol) increase, which indicated the satisfied extraction performance as showed in Fig. 2. Dispersive interactions in DESs with long alkyl chains could explain this [50]. Most non-ionic DESs have lower viscosity than ionic DESs, and the viscosity decreases as the temperature increases, allowing for faster mass transfer of targets between the extraction solvents and sample matrices [40,50].

2.2. Structure of DESs

2.2.1. Structure of ionic DESs

Since Abbott et al. discovered the deep eutectic phenomenon, research on this novel solvent has progressed. DESs are typically prepared from non-toxic materials and are formed in a different chemical process [38]. Ionic DESs are traditionally divided into four types: Type I, a quaternary ammonium salt and a metal chloride; Type II, a quaternary ammonium salt and a metal chloride hydrate; Type III, a quaternary ammonium salt and a HBD (such as an amide, carboxylic acid, or polyol), Type IV, consisting of a metal chloride hydrate and HBD [51]. ChCl-based ionic DESs are commonly mixed with hydrogen bonding donors, such as carboxylic acid, urea, citric acid, succinic acid and glycerol [52]. A special type of DESs being referred to as natural DESs (NADESs), are comprised of relatively inexpensive and easily accessible components such as non-toxic quaternary ammonium salts (e.g., ChCl) and naturally derived uncharged hydrogen-bond donors (e.g., vitamins, amines, sugars, alcohols, carboxylic acids) [53]. As research progresses, the ionic DESs can be considered mixtures of certain salts (HBA) and a HBD (Fig. 3).

2.2.2. Structure of non-ionic DESs

In 2019, a type V deep eutectic solvents composed of non-ionic species such as thymol and menthol was proposed (Fig. 3). The solvent could be reused and regenerated by evaporation. This unique advantage can solve the disadvantage that conventional ionic DESs cannot be recovered by evaporation [26]. Furthermore, NADESs also contains a large amount of non-ionic DESs. There are also NADESs composed of natural non-ionic hydrophobic components, such as natural perfumes (DL-menthol) [41], long-chain alkanols [50], sugars [54], and fatty acids [55]. The HBA and HBD in non-ionic DESs can not be distinguished in the same way as in ionic DESs [26].

2.3. Synthesis methods of DESs

There are four standard methods for preparing deep eutectic solvents: heating, grinding, evaporation, and freeze-drying. The

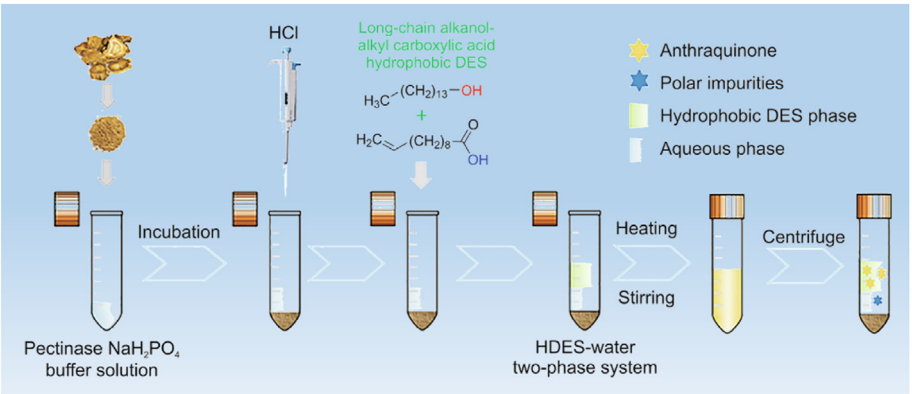

Fig. 2. Schematic procedure of long-chain alkanol-alkyl carboxylic acid hydrophobic DESs-water two-phase system for one-pot extraction of weakly polar anthraquinones from Rhei Radixet Rhizoma (Reproduced with permission from Ref. [50]).

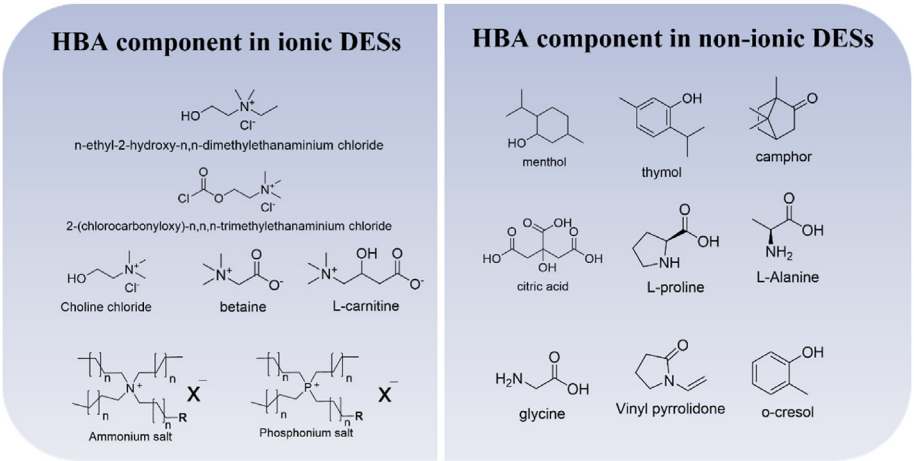

Fig. 3. Structure of typical HBA component in ionic and non-ionic DESs.

complexation of a halide salt, which acts as a hydrogen-bond acceptor, and a hydrogen-bond donor results in the formation of DESs [38].

(1) Heating method, as the most commonly used synthesis approach for ionic and non-ionic DESs, was first proposed by Abbott et al., in 2003 [12,56,57]. At a suitable temperature below 100 °C (usually 80 °C), the mixture was stirred until a clear homogeneous liquid formed with a typical mixing time of approximately 60–90 min [58]. If not stirring or just stirring, it can be divided into another method [59]. No additional solvent is required during the heating and stirring, no traditional reaction occurs, and no purification steps are required [51].
(2) With the grinding method, the mixed compounds can be ground at room temperature until a clear and stable liquid is formed, which is useful when the composition of DESs is in equal amounts [59]. Despite its inconvenience, the obtained DESs is purer than the products of common synthesis using the heating method because such impurities are avoided [40]. The grinding method may be preferred to prepare ionic DESs rather than non-ionic DESs because of higher viscosity and differences in experimental thermophysical properties [40,50,60].
(3) The evaporation method is appropriate for preparing highly viscous DESs, such as sugar-based DESs, to overcome the problem of stirring difficulties [59]. Extra water is added to the mixture and then evaporated at 323 K using a rotary flash evaporator after dissolution. The gained DESs is dehydrated in a silica gel desiccator to maintain a constant mass [40].
(4) Unlike the other three methods discussed above, freeze-drying is rarely used because it cannot eliminate all water molecules from the DESs structure. With this method, after mixing each component, the mixture is frozen and then freeze-dried at various temperatures until a clear, viscous liquid forms [40].

3. Applications for extraction of natural herbal medicine

3.1. Flavonoids

Flavonoids with carbon numbers C6–C3–C6 have antioxidant and anticancer activity and may be useful as potential therapies for bladder cancer [61,62]. Previously, commonly used organic solvents were used as extraction solvents because of insolubility of flavonoids [63]. On the other hand, considering the time-consuming, non-ecofriendly, and high cost, DESs have been proven as the prospective green solvent than traditional solvents for extracting multiple flavonoids from natural herbal medicine [13,38,64–66].

Studies of DESs extracting plant flavonoids increase each year progressively [67–75], as shown in Table 1. For example, Meng et al. examined the efficacy of eight different ionic DESs on flavonoids

Table 1
The representative application of ionic and non-ionic DESs for extraction of flavonoids from natural herbal medicine.

Analytes	Sample matrix	DESs composition(mole ratio)	Method of extraction	Yield	Recovery rate	Ref
Flavonoids by ionic DESs						
Quercetin and myricetin	Ginkgo biloba	ChCl/OxaA/EG (1/1/3)	HRE[1], solid/liquid: 100 mg/mL, 60 °C, 30min, 50% water (v/v)	1.40 and 1.11 mg/g		[64]
Myricetin, morin and rutin	*Lycium barbarum* L. fruits	ChCl/p-toluene sulfonic acid (1:2)	UAE, solid/liquid: 20 mg/mL, room temperature, 1.5 h	57.2, 12.7 and 9.1 mg/g	96%, 84.1%, 93.9%	[80]
Quercetin, naringenin, kaempferol and isorhamnetin	*Pollen Typhae*	ChCl/1,2-propanediol (1:4)	UAE, solid/liquid: 50 mg/mL, 60 °C, 35 min, 30% water	0.383, 0.048, 0.391, 3.149 μg/mg	86.87%, 98.34%, 97.64% and 98.89%	[76]
Rutin, quercetin-3-O-glucoside, quercetin, kaempferol and isorhamnetin	sea buckthorn leaves	1,4-butanediol/ChCl (3:1)	MAE[2], liquid/solid: 21 mL/g, 64 °C, 17 min	total maximum extraction yields:20.820 mg/g; scale-up extraction yields: 8.972, 1.821, 9.104, 0.445 and 0.493 mg/g	72.36–84.99%	[78]
Myricitrin, quercitrin; amentoflavone and hinokiflavone	Platycladi Cacumen	ChCl/Laevulinic Acid (1:2)	UAE, solid/liquid: 25 mg/mL, 50 °C, 30 min, 10% water (v/v)		92.07%, 98.92%, 97.19% and 77.44%	[86]
Rutin	Tartary buckwheat hull	ChCl/Glycerol (1:1),	UAE (200 W), solid/liquid: 40 mg/mL, 40 °C, 1 h, 20% water (w/w)	9.5 mg/g	95%	[87]
Rutin, nicotiflorin, narcissin, quercetin, kaempferol and isorhamnetin	*Flos Sophorae Immaturus*	ChCl/1,4-butanediol (1:2),	MAE (600W), liquid/solid: 26 mL/g, 60 °C, 20 min, 25% water (v/v)	116.78, 15.01, 23.85, 27.59, 3.09 and 3.33 mg/g	75.5%–84.1%	[65]
Flavonoids	*Hibiscus sabdariffa* L.	ChCl/oxalic acid (1:1)	MAE, liquid-solid: 1:30 mL/mg, 75 °C, 55% water (v/v)	6.00 ± 0.09 mg/g		[66]
Scutellarin, baicalin, baicalein, wogonoside, wogonin, and oroxylin, A	*Scutellaria baicalensis*	betaine/acetic acid (1:4)	UAE, solid/liquid: 10:1 mg/mL, 52 °C, 23 min, 40% water (v/v)			[73]
Luteolin and apigenin	*Achillea millefolium* L	ChCl/lactic acid (1:2)	UAE, solid/liquid: 500 mg/10 mL, 50 ± 1 °C, 30 min, 25% water (w/w)			[74]
Rutin	Chokeberry (*Aronia melanocarpa*)	ChCl/D-(−)-fructose/water (2:1:1)	UAE, solid/liquid:1:5 g/mL, 35 °C, 20 min	4.71 ± 0.33 mg rutin g^{-1} DW		[35]
Total flavonoids	rhizomes of *Polygonatum odoratum*	ChCl/lactic acid (1:2),	Liquid/solid ratio of 22 mL/g, 51 °C, 21 min, 27% water (v/v)	11.47 ± 0.35 mg/g	93.98%	[79]
Total flavonoids	*Ixora javanica* flower	ChCl/propylene glycol (1:1)	UAE, solid/liquid ratio: 1:25 g/ml, room temperature, 40 min, 25% water (v/v)	89.732 mg QE g^{-1} dried flowers		[75]
Rutin	*Eucommia ulmoides* Oliver leaves	ChCl/1,4-butanediol/Vc(1:1:0.2, mol/mol/mol), (Vc: ascorbic acid)	MAE, solid/liquid ratio:1:18.5 g/mL, 53 °C,20 min, 20% water	1.143 mg/g	74.85%	[88]
Apigenin	Olive leaf	ChC/fructose/water (CFW) (5:2:5)	UAE, solid/liquid: 200 mg/mL, 75 °C, 60 min	12.75 ± 0.6 mg apigenin equivalent g^{-1} dw		[67]
Quercetin	*Artemisia annua* Leaves	HFIP-ChCl (1:1)/Menthol-N_{8881}Cl (2:1) biphasic system (1:1) (v/v)	Solid/liquid: 15/1, 20 °C, 30 min	5.5 mg/g	86.5%	[68]
Eucommiol, rutin, kaempferol-3-O-sambubioside, isoquercitrin, kaempferol-3-O-rutinoside, astragaline	*Eucommia ulmoides* leaves	ChCl/L-(+)-ascorbic acid (2:1)	MAE, liquid/solid: 25 mL/g, 75% water (v/v)	total content of flavonoids: 12.55 mg/g	97.59%, 87.33%, 86.57%, 82.15%, 89.28% and 80.75%	[70]
Orexin B, orexin A, baicalein and chrysin	the seeds of *Oroxylum indicum*	ChCl/1,4-butanediol (1:4)	Tissue-smashing extraction, solid/liquid: 20:1 mg/mL, 1 min, 40% water (v/v)	23.36 ± 1.25 24.08 ± 2.01 13.14 ± 0.82 3.46 ± 1.63 mg/g	90.17%, 84.14%, 78.34% and 98.18%	[77]
Linarin	*Chrysanthemum indicum* L. flower	ChCl/ethylene glycol (1:2)	UAE (340 w), liquid/solid: 32 mL/g, room temperature, 32 min, 30% water (v/v)	14.23 mg/g	81.55%	[71]
Flavonoids	*Lippia citriodora*	ChCl/lactic acid (1:2)	MAE, 63.68 °C, 17.08 min, 32.19% water (v/v)	9.02 mg/g		[72]
Flavonoids by non-ionic DESs						
Icarrin, IcarisidII, Epimcdin A, Epimcdin B and Epimcdin C	*Herba Epimedii*	L-proline/ethylene glycol (1:4),	UAE, 45 min, solid/liquid: 50 mg/mL, room temperature, 30% water (v/v)	Highest total yield of 19 batches:15.978 ± 0.696; 1.525 ± 0.053, 6.176 ± 0.346, 3.823 ± 0.115, 6.064 ± 0.190, 0.432 ± 0.025 mg/g	88.5–107.7%	[84]
				32.83, 8.80 mg/g	88.5–107.7%	[81]

(*continued on next page*)

Table 1 (*continued*)

Analytes	Sample matrix	DESs composition(mole ratio)	Method of extraction	Yield	Recovery rate	Ref
Hydroxysafflor yellow A, anhydrosafflor yellow B	*Carthamus tinctorius* L.	L-Proline/acetamide/water (1:1:2)	UAE (200 W), solid/liquid: 200 mg/mL, 50 °C, 30 min			
(+)-catechin, vicenin-2, orientin, rutin, hyperoside, kaempferol-3-O-rutinoside, isorhamnetin 3-O-glucoside, quercetin; apigenin, kaempferol, (−)-epigallocatechin	*Moringa oleifera* L. leaves	L-proline/glycerol (2:5),	Solid/liquid:12.5:1, 15 min, 40 °C, 37%water (v/v)			[17]
Hydroxysafflor yellow A, anhydrosafflor yellow B	safflower	L-proline-acetamide (1:1)	UAE (200 W), solid/liquid:200 g/1 mL, 50 °C, 30 min, 50% water (v/v)	32.83 and 8.80 mg/g	92.08 −109.14%	[81]
Scutellarin, baicalin, wogonoside, baicalein and wogonin	*Radix scutellariae*	L-proline/glycerol (1: 4)	UAE, solid/liquid: 20 mg/1.2 mL, vortex for 5 min, room temperature, 42 min, 33.3% water	74.05 ± 1.89, 176.3 ± 3.06, 35.96 ± 0.38, 1.76 ± 0.04 and 0.60 ± 0.02 mg/g	97.1−100.7%	[83]
Daidzin	*Pueraria candollei* var. *mirifica* (PM) root	Water/sucrose/glucose: fructose, (18:3:18:22w/w/w/w)	sonication-assisted extraction (37 Hz), solid/liquid:150:1.5 mg/mL, ambient temperature, 3 h, 50 %water (v/v)	75.8 ± 3.67 μg/mL	98.3−106%	[54]
Flavonoids	*Acanthopanax senticosus*	Glycerol/levulinic acid (1:1)	UAE (500W), solid/liquid:1:18 g/mL, 55 °C, 73 min, 28% water (v/v), recover with AB-8 resin	23.928 ± 0.071 mg/g	71.56 ± 0.256%	[85]
Luteolin 7-glucuronide, luteolin and apigenin	*Lavandula pedunculata* subsp. *lusitanica* (Chaytor) Franco	Proline/lactic acid (1:1); ChCl/urea (1:2)	UAE, 0.25:10 (w/v), 50 °C, 60 min,			[89]
Flavonols	saffron processing waste	L-lactic acid/glycine (5:1)	Liquid/solid ratio: 60 mL/g, 50 −60 °C, DESs concentration: 55% (w/v), 800 rpm,	Total polyphenols yield: 132.43 ± 10.63 mg gallic acid equivalents per g		[82]

1: Heat reflux extraction; 2: Microwave-assisted extraction.

extracted from *Pollen Typhae* by ultrasound-assisted extraction (UAE). The mixed solvent with 70% ChCl-based DESs (ChCl/1,2-propanediol) and 30% (v/v) water had a the higher extraction yield for flavonoids, such as quercetin, naringenin, kaempferol, and isorhamnetin, than other DESs and 75% aqueous ethanol and methanol [76]. In addition, the fast extraction of main flavonoids (baicalein, chrysin, and orexin A and B) in the seeds of *Oroxylum Indicum* was achieved by DESs (ChCl/1,4-butanediol) with a mole ratio of 1:4 [77]. In 2018, Cui et al. synthesized 12 kinds of ionic DESs, which were used as extraction solvents to separate five main flavonoids (rutin, quercetin-3-O-glucoside, isorhamnetin, quercetin, and kaempferol). As a kind of tailor-made solvent, DESs revealed the satisfactory extraction capacity towards flavonoids with the yield of 8.972, 1.821, 0.493, 9.104, and 0.445 mg/g under optimal conditions. Compared with traditional technology, the extraction efficiency of the technology proposed in this case is 1.3−2.4 times that of the traditional extraction technology. Furthermore, 72.36% of the target flavonoids in the DESs extract were purified and recovered using porous resin AB-8. The realization of this technology can provide a feasible reference for DESs as an extraction solvent in industrialization [78]. In addition, the flavonoids were extracted from the rhizomes of *Polygonatum odoratum* using ionic DESs, ChCl/1,2- propanediol with a mole ratio of 1:4. The extraction yield of total flavonoids was 11.47 mg/g, which was comparable to the conventional method [79]. Ali et al. used a promising method based on ionic DESs (ChCl/p-toluene sulfonic acid (1:2)) to obtain high extraction yields of flavonoids from *Lycium barbarum* L. fruits. The yield of myricetin, morin and rutin are 57.2 mg/g, 12.7 mg/g, and 9.1 mg/g, respectively [80].

There are also some reports on non-ionic DESs extracting flavonoids [17,81,82]. Xiong et al. synthesized a variety polyol based ionic DESs consisting of ChCl, amino acids, organic acids, and polyols. According to the results, there was no significant difference between the method from the Chinese Pharmacopoeia (2015 edition). They proposed an ionic DESs-based extraction method toward flavonoids (scutellarin 74.05 ± 1.89 mg/g, baicalin 176.3 ± 3.06 mg/g, wogonoside 35.96 ± 0.38 mg/g, baicalein 1.76 ± 0.04 mg/g, and wogonin 0.60 ± 0.02 mg/g) from *Radix scutellariae* [83]. Compared with ionic DESs, a non-ionic DESs consisting of L-proline and ethylene glycol with a molar ratio of 1:4 exhibited excellent performance in extracting five flavonoids (Icarrin, IcarisidII, Epimcdin A, Epimcdin B, and Epimcdin C) from *Herba Epimedii*. The recoveries for the above flavonoids ranged from 88.5 to 107.7%. Compared with the standard extraction method on Icarin from Chinese Pharmacopoeia (2015 edition), this green method had 80% solvent consumption and a 25% shorter extraction time [84]. In 2021, Tong et al. reported another kind of non-ionic DESs composed of L-proline/acetamide (1:1) containing 50% water selected as the optimal extraction solvent for the extraction of two flavonoids (hydroxysafflor yellow A, anhydrosafflor yellow B) from *Carthamus tinctorius* L. In this case, ultrasonic was used as an assistant ability in breaking the plant cell walls during the extraction process and it obtained the maximum extraction yields of hydroxysafflor yellow A and anhydrosafflor yellow B (32.83 and 8.80 mg/g) [81]. In 2022, Zhang et al. extracted bioflavonoids from *Acanthopanax senticosus* using an ultrasonic-assisted non-ionic DESs extraction method. The extraction efficiencies of the DESs consisting of glycerol and levulinic acid with a molar ratio of 1:1 were significantly higher than those of the traditional ultrasonic-assisted ethanol extraction, with yield and

recovery reaching 23.928 ± 0.071 mg/g and 71.56 ± 0.256%, respectively [85]. According to the data compiled in Table 1, both ionic and non-ionic DESs have good extraction capabilities for flavonoids. However, the advantage of ionic DESs is that its viscosity is generally lower than that of non-ionic DESs. Ionic DESs can provide better mass transfer efficiency during the extraction process.

3.2. Phenolics

Phenolic compounds are comprised of one or more hydroxyl groups that are linked to an aromatic ring. Several phenolic compounds exist, such as simple phenol, phenolic acid, polyphenol, coumarins, and cinnamic acid. Phenolic compounds have attracted the interest of scientists because of their abundant supply in nature and antibacterial, anti-inflammatory, antioxidant, and antitumor properties [63].

DESs have been used extensively to extract phenolics from nature sources [90–97], as shown in Table 2. Various binary and ternary DESs were investigated in 2019 for the simultaneous extraction of four phenolic acids, e.g., 3-caffeoylquinic acid, 3,4-di-O-caffeoylquinic acid, 3,5-di-O-caffeoylquinic acid, and 4,5-di-O-caffeoylquinic acid from *Artemisia argyi* leaves. The ionic DESs consisting of ChCl, malic acid, and urea with a molar ratio of 2:1:2, outperformed common organic solvents and other DESs in the simultaneous extraction of four phenolic acids [98]. Fanali et al. showed that DESs of ChCl/lactic acid (1:2), with 35% water (v/v) at 80 °C for 60min coupled with an ultrasound-assisted method was the most efficient DESs-based extraction of phenolics from *Corylus avellana* L, with a recovery of more than 39% [42]. For instance, in 2021, a study reported a microwave (MW)/DES-assisted (MWDA) extraction process for obtaining valuable compounds from chestnut shell waste (CSW), which realized the fast, cheap and tunable improved extraction of food waste [99], as showed in Fig. 4. Moreover, in a study, the extraction ability of ChCl/acid-based DESs was compared with ethanol, the optimal extraction conditions for DESs extracted 15% more phenolic compounds than ethanol with advantages of environment friendly and non-toxicity, as showed in Fig. 5 [100].

Furthermore, Barbieri *et a.l* used a DESs formed by mixing 1,2-propanediol/ChCl (1:2 v/w) and 10% water as an extraction solvent to extract phenolics from *Rosmarinus officinalis* L. The antioxidant capacity, and kinetic degradation were evaluated, and all DESs-based extracts showed higher antioxidant capacity than the alcohol extract [93]. Recently, an ionic DESs composed of ChCl:1,4-butanediol (1:6) prepared with 10% water (v/v) was used to extract curcuminoids from turmeric, such as curcumin, bisdemethoxycurcumin, and demethoxycurcumin. The extraction yields (TPC:55.86; 46.70 ± 0.55, 46.14 ± 0.82, 10.63 ± 0.35) were the highest reported at that time [101]. Moreover, the ternary ionic DESs consisting of ChCl, 1,4-butanediol, and ascorbic acid with the appropriate molar ratio revealed outstanding performance in the extraction of geniposidic acid from *Eucommia ulmoides* Oliver leaves. The yield was 1.4-fold higher than that of the traditional method. The extraction yield and recovery of chlorogenic acid obtained using the proposed ionic DESs-based extraction method were 6.897 mg/g and, 78.75%, respectively [88]. In 2022, Luo et al. reported that an ionic DESs consisting of ChCl and L-(+)-ascorbic acid at a molar ratio of 2:1 with 75% (v/v)water combining microwave-assisted extraction showed higher efficiency (90.66% recovery) than with a 50% methanol solution [70]. In addition, ten different ionic DESs systems were explored to extract phenolics with varying polarities from *Lavandula pedunculata* subsp. *lusitanica* (Chaytor) Franco. The non-ionic DESs (proline-lactic acid, 1:1) and ionic DESs (ChCl-urea, 1:2) had superior extractability for the total phenolic compounds compared to regular solvents. The obtained extracts exhibited enzyme inhibitory capacity and considerable ability to inhibit enzymes during this proposed method [89]. In 2019, Rajha et al. reported an innovative process to improve the recovery of polyphenols in pomegranate peels combining a new IR technology, which showed the highest antioxidant and antiradical activities [102]. In addition, several studies have examined the extraction of phenolic compounds from natural herbal medicine using ionic DESs and reported exceptional extraction performance [103–105]. For instance, Yang et al. reported a three-phase extraction system based on ionic DESs, which realized the separation of Rosmarinus acid (hydrodynamic) and Cardiovascular acid (hydrophobic) by temperature induced independent stratification between each phase [106], as showed in Fig. 6.

Anthocyanins are natural colorants associated with phenolic compounds. The extraction of phenolic compounds from *Lycium ruthenicum* Murr. fruit using a DESs comprised of ChCl/1,2-propanediol (1:2) with 10% of water (v/v) exhibited satisfactory efficiency for fifteen anthocyanins. The maximum extraction yield of total anthocyanins reached 4.45 ± 0.07 mg/g under the optimal extraction conditions: 52 °C, 45 min, and a liquid/solid ratio of 20:1 [44]. In one study, the yield of anthocyanins extracted from fresh mulberry using the ionic DESs ChCl/citric acid/glucose with a molar of 1:1:1 coupled with high-speed homogenization and cavitation-burst extraction (HSH-CBE) was increased by 24% compared to those using conventional organic solvents. Furthermore, ionic DESs had higher anthocyanin extraction stability than typical organic solvents, which is advantageous for anthocyanin assessment and retention [107]. Similarly, many studies have extracted anthocyanins from plants, such as *Artemisia annua* Leaves [68], *Nitraria tangutorun* Bobr. Fruit [108], and *Hibiscus sabdariffa* L [66]. The flow chart of some technologies is shown in Fig. 7.

Some studies on extracting phenolics with non-ionic DESs [109–113]. For example, Wang et al. examined the extraction yield of tailor-made DESs on the polyphenols from fig leaves. A ternary non-ionic DESs consisting of glycerol, xylitol, and D-(−)-fructose combined with microwave-assisted extraction obtained more polyphenolics than some other DESs and more than with conventional methanol [114]. In 2020, a polymerization based on molecular imprinting technology, assisted by DESs as a functional monomer, realized the selective recognition and separation of catechins in green tea [115]. Furthermore, classical extraction of cannabis bioactive compounds, such as cannabidiol (CBD) and cannabidiolic acid, is a risky operation involving organic solvents. Fortunately, Tiago et al. discovered that the yield of cannabidiol and cannabidiolic acid extracted from cannabis with non-ionic DESs (menthol-lauric acid, 2:1) was approximately 11.07 mg/g, which was more efficient than all other tested DESs and that of ethanol (8.19 ± 1.7 mg/g). The high extraction capacity and lack of toxicity make menthol-based DESs ideal for extracting the phenolics in cannabis [116]. A novel non-ionic DESs (Neoteric glycerol/L-alanine (5:1), 70% aqueous mixtures (w/w)) was synthesized for the extraction of polyphenols from hops. The results showed that temperature changes were essential to the extraction's efficiency during the extraction process. The extraction rate should be slowed at higher temperatures when using ultra-assisted extraction [117]. Bentley et al. examined the extraction of anthocyanins from *Myrothamnus flabellifolia*. The optimal extraction solvents non-ionic DESs, consisted of sucrose, citric acid, and water with a molar ratio of 1:1:10 [118]. According to the current data summary, ionic DESs generally adds a portion of water in the process of extracting phenolic compounds to improve extraction efficiency. However, non-ionic DESs does not require water to assist in improving the extraction efficiency of phenolic components due to its multi hydroxyl structure as both its hydrogen bonding donor and hydrogen

Table 2
The representative application of ionic and non-ionic DESs for extraction of phenolics from natural herbal medicine.

Analytes	Sample matrix	DESs composition(mole ratio)	Method of extraction	Yield	Recovery rate	Ref
Phenolics by ionic DESs						
Phenolics	*Carya cathayensis Sarg.* peels	ChCl/Malic acid (1.5:1)	UAE (460 W), liquid/solid: 40:1 mL/g, 15 min, 80 °C	60.84 ± 0.48 mg GAE/g		[90]
Phenolic	*Juglans regia* L.	ChCl/butyric or phenylpropionic acid (1:2)	HAE[1], solid/liquid: 30 mg/mL, 50 °C, 60 min, 20% water (v/v) (w/w), 600 rpm, protection from light	140 g/L		[91]
Bael polyphenols	*Aegle marmelos*	ChCl/oxalic acid (1:1)	UAE, solvent/DESs 50:1 mL/g dry weight, 80 °C, 25% water,	80.502 mg GAE/g dw		[92]
Rosmarinic acid, caffeine, 7-methylrosmanol, rutin, naringin and ferulic acid	*Rosmarinus officinalis* L. leaves	1,2-propanediol/ChCl (1:2) (v/w)	UAE, 40 ± 1 °C, 2 h, solid/DESs: 150:2.85 mg/mL, 10% water (w/w)	Total extraction yields: 62.21 ± 3.85 mg AG/g		[93]
3-caffeoylquinic acid, 3,4-di-O-caffeoylquinic acid, 3,5-di-O-caffeoylquinic acid, and 4,5-di-O-caffeoylquinic acid	*Artemisia argyi* Leaves	ChCl/malic acid/urea (2:1:2)	Liquid/solid: 57.5 mL/g, 23.5 min, 54% water (v/v)	22.80 mg/g		[98]
Phenolics	*Corylus avellana* L	ChCl/lactic acid (1:2)	UAE, solid/liquid: 1:25 g/mL, 80 °C, 60 min, 35% water (v/v)		>39%	[42]
NCA, CA, CCA, CFA, RU, IS, AS	mulberry (*Morus alba* L.) leaves	ChCl/Glycerol (1:2)	MAE, liquid/solid: 20 mL/g, 66 °C, 18 min, 20% water (v/v)	Total yield: 8.352; 0.240, 4.507, 0.342, 0.286, 1.468, 0.971 and 0.538 mg/g	79.89%, 83.77%, 80.29%, 82.14%, 77.81%, 79.95% and 81.05%	[94]
Gingerols	ginger	Betaine/1,3-butanediol (1:4); L-carnitine/ Triethylene glycol (1:4); L-carnitine/1,3-butanediol (1:4)	UAE, liquid/solid: 30/1, 50 °C, 30 min, 25% water (v/v)	4.41 mg/g		[95]
Gallic acid	orange peel	ChCl/EG (1:4)	Solid/liquid: 1:10, temperature: 333.15 K, 100 min, 10 wt% water	3.61 (GAE/g OP)		[96]
Phenolic acids	*Hibiscus sabdariffa* L.	ChCl/oxalic acid (1:1)	MAE, liquid/solid: 1:30 mL/mg, 75 °C, 55% water (v/v)	24.41 ± 0.32 mg/g		[66]
Phenolics	peppermint leaves (*Mentha piperita* L)	ChCl/D-(+)-glucose (5:2)	UAE, solid/liquid: 100:1 mg/mL, ambient temperature, 45 min	TPC and TFC of Menthol different between the countries,55.23–98.27 mg/g and 7.30–21.05 mg/g; Korea sample: 98.27 (±7.81) TPC (mg GAE g^{-1} dried)		[97]
Curcuminoid: curcumin, bisdemethoxycurcumin, demethoxycurcumin	turmeric	ChCl/1,4-butanediol (1:6)	UAE, solid/liquid:1:15 g/mL, ambient temperature, 2 h, 10% water (v/v)	Total yield: 55.86; 46.70 ± 0.55, 46.14 ± 0.82, 10.63 ± 0.35 mg/g	56%	[101]
Total phenols	*Chamaenerion angustifolium* (L.) Scop. (fireweed)	ChCl/citric acid	UAE (120 W, 40 kHz), solid/liquid: 1:10 (w/v), 58 °C, 35 min, 70 wt% water			[103]
Rosmarinic acid and carnosic acid	Rosmarinus officinalis leaves	ChCl/LA/[BMIM]PF6/H2O (1/2/1) (v/v/v)	UAE (500 w), liquid/solid: 20 mL/g, 60 °C, 20 min	7.06 and 17.74 mg/g	88.97%, 97.46%	[106]
Chlorogenic acid and dicaffeoylquinic acid isomers	*Achillea millefolium* L	ChCl/lactic acid (1:2)	UAE, solid/liquid: 500:10 mg/mL, 50 ± 1 °C, 30 min, 25% water (w/w)			[74]
Gallic acid	Chokeberry (*Aronia melanocarpa*)	ChCl/D-(−)-fructose: water (2:1:1)	UAE, solid/liquid: 1:5 g/mL, 35 °C, 20 min	36.15 ± 3.39 mg gallic acid g^{-1} dry weight (DW)	70%–97%.	[35]
Geniposidic acid	*Eucommia ulmoides* Oliver leaves	ChCl/1,4-butanediol/Vc (1:1:0.2, mol/mol/mol), (Vc: ascorbic acid)	MAE, solid/liquid:1:18.5 g/mL, 53 °C, 20 min, 20% water (v/v)	6.897 mg/g	78.75%	[88]
Gallic acid, caffeic acid	Olive leaf	ChCl/ructose/water (CFW) (5:2:5); glucose/fructose/ water (GFW) (1:1:11)	UAE, liquid/solid: 50 mL/g, 75 °C, 60 min	187.31 ± 10.3 mg gallic acid equivalent g^{-1} dw; 112.77 mg kg^{-1} dw		[67]
Polyphenols	pomegranate peels	kaempferol and quercetin: Lactic acid/ChCl (3:1), protocatechuic acid/ChCl/ Fructose (1.9:1), caffeic acid: Malic acid/Glucose/ Glycerol (1:1:1)	IR[2], liquid/solid: 10 mL/g, 50 °C, 90 min, 30% water (v/v)	152 mg/g DM		[102]
Carnosol	*Salvia officinalis*	ChCl/lactic acid (1:2)	Solid/liquid: 50:1 mg/mL, 25 °C, absorbed for 3 h, desorbed for 2 h, 10% water (v/v), 1500 rpm,		96.63 ± 0.04%	[104]
Vitamin E	red palm biodiesel	K_2CO_3/glycerol (1:6)	Biodiesel/DESs (1:3) (mass ratio), 3 h, 400 rpm			[105]
Geniposidic acid	*Eucommia ulmoides* leaves	ChCl/L-(+)-ascorbic acid (2:1)	MAE, liquid/solid: 25 mL/g, 75% water (v/v)	12.55 mg/g	90.66%	[70]
			UAE, 50 °C, 60 min, 0.25:10 (w/v),	56.00 ± 0.77 mg GAE/g dw		[89]

Table 2 (*continued*)

Analytes	Sample matrix	DESs composition(mole ratio)	Method of extraction	Yield	Recovery rate	Ref
Rosmarinic acid, ferulic acid, salvianolic acid B and so on	*Lavandula pedunculata* subsp. *lusitanica* (Chaytor) Franco	Proline/lactic acid (1:1); ChCl/urea (1:2)				
15 anthocyanins	*Lycium ruthenicum* Murr. fruit	ChCl/1,2-propanediol (1:2)	Liquid/solid: 20:1, 52 °C, 45 min, 10% water (v/v)	4.45 ± 0.07 mg/g	>95%	[44]
Anthocyanidins	*Artemisia annua* Leaves	HFIP-ChCl (1:1)/Menthol-N_{8881}Cl (2:1) biphasic system (1:1) (v/v)	Liquid/solid:15/1, 20 °C, 30 min	8.9 mg/g (transferred to the lower layer (HFIP-ChCl with 1:1 mol ratio))	88.1%	[68]
Anthocyanins	*Nitraria tangutorun* Bobr. fruit	ChCl/1,2-propanediol	UAE, solid/liquid: 1:15 g/mL, 50 °C, 30 min, 25% water (w/w)	Total anthocyanins yield: 1.413 ± 0.054 mg/g	>95%	[108]
Anthocyanins	fresh mulberry	ChCl/citric acid/glucose (1:1:1)	Liquid/solid: 22 mL/g, 30 min, 45 °C, 30% water (v/v), extraction two times	6.05 mg/g (fresh weight)		[107]
Anthocyanins, phenolic acids, flavonoids, other polar compounds	*Hibiscus sabdariffa* L.	ChCl/oxalic acid (1:1), 55% water	MAE, liquid/solid: 1:30 mL/mg, 75 °C	10.43 ± 0.92, 24.41 ± 0.32, 6.00 ± 0.09, 44.25 ± 1.29 mg/g		[66]
Phenolic		ChCl/oxalic acid dihydrate (1:1)	MAE, solid/liquid: 1:10, 85 °C, 60min, 28.26 wt %			[99]
Phenolic	Olive leaves	ChCl/acetic acid (1:2)	HAE, 85 °C, 3h, 50% water	470.03 mg/kg		[100]
Phenolics by non-ionic DESs						
gallic acid, p-hydroxybenzoic acid, rosmarinic acid	*Moringa oleifera* L. leaves	L-proline/glycerol (2:5)	Solid/liquid:12.5/1, 40 °C, 15 min, 37% water (v/v)			[17]
21 phenolics	*Peumus boldus* leaves	L-proline/oxalic acid (1:1)	Solid/liquid: 10/1, room temperature, 20 min, 20% water (v/v)			[33]
Polyphenols	*Peumus boldus* leaves	l-Proline/Oxalic acid (1:1)	Heating + stirring extraction (340 rpm), solid/liquid: 5:1 mg/mL, 50 °C, 50 min, 20%water (v/v)	TPC: 179.442 ± 3.79 mg g^{-1} GAE dw		[109]
Phenolics	*Hibiscus sabdariffa*	ethylene glycol/citric acid (1:4)	MAE (550 W), 35 mL DESs, 3min, 50% water (v/v)	31.897 mg-GAE/g-DH		[110]
Rosmarinic acid, ferulic acid, salvianolic acid B and so on	*Lavandula pedunculata* subsp. *lusitanica* (Chaytor) Franco	Proline/lactic acid (1:1)	UAE, 0.25:10 (w/v), 60 min, 50 °C	56.00 ± 0.77 mg GAE/g dw		[89]
Polyphenol	*Humulus lupulus* (Hop)	Neoteric Glycerol/L-Alanine (5:1)	UAE, liquid/solid: 35 mL/g, 50 °C, 150 min, 70% water (w/w), 500 rpm	118.97 ± 8.27 mg gallic acid equivalents per g of dry mass		[117]
Polyphenols, flavonols	*Sambucus nigra* flowers (elderberry flowers)	L-lactic acid/glycine (5:1)	Liquid/solid: 60 mL/g, 80 °C, DESs/water (85% w/v), 200 rpm, ultrasound pretreatment	174.73 ± 2.62 mg gallic acid equivalents per g dry matter		[111]
Cannabidiol and cannabidiolic acid	*Cannabis sativa* L. Flowers and leaves	Glucose L (+)/Lactic Acid (1:5); Menthol-Lauric Acid (2:1)	UAE (100 W), solid/liquid: 1:10 (W/W), 45 min, 60 °C	7.76 ± 1.1; 11.07 ± 0.37 mg/g		[116]
Curcuminoids (BDMC, DMC, CUR)	*Curcuma longa* L.	Citric acid/glucose (1:1)	Solid/liquid: 0.1:10 g/mL, 50 °C, 30 min, 15% water (v/v)	16.5, 15.12, and 21.18 mg/g	BDMC (88.5%), DMC (94.4%), and CUR (93.2%)	[45]
caffeoylmalic acid, psoralic acid-glucoside, rutin	Fig (*Ficus carica* L.) leaves	Glycerol/xylitol/D-(−)-Fructose (3:3:3)	MAE, liquid/solid: 17.53, 64.46 °C, 24.43 min	6.482, 16.34, 5.207 mg/g	79.2%, 83.4%, 85.5%	[114]
Catechins (C, EC, EGC, ECG, and EGCG)	Green tea	Vinyl pyrrolidone/malonic Acid (1:1)	Fe3O4@MoS2@DESs-MIP: methanol-acetic acid (9:1) (v/v), Fe_3O_4@MoS_2 (12.9 g $FeCl_3 \cdot 6H_2O$ and 2.94 g sodium acetate) microspheres modified by MPS, then used to absorbed extracts	25.5, 16.7, 16.9, 20.9, 70.5 mg/g	31.8%, 13.5%, 21.1%, 26.2%, >98%	[115]
Catechin, ellagic and p-hydroxy benzoic acids	*Humulus lupulus* L	lactic acid/sucrose (4:1), lactic acid/urea (3:1), lactic acid/glycine (3:1)	UAE, solid/liquid: 1:15 g/mL, room temperature, 30 min, 20% water, in the dark; another 30 min in an ultrasound bath, 40 kHz, 25 °C, 300 rpm	total polyphenol yield: 1630.36 to 704.15 μg/g		[112]
DS I, TS I, CS, NQ A, TS IIA, AF, BT, GT, IG, SP, and CA	*Rosmarinus officinalis* leaves, *Ginkgo biloba* leaves	D,L-Menthol/D,L-Lactic acid (1:2)	UAE (350 W), solid/liquid: 1:30 g/mL, 25 °C, 40 min (DSI、TSI、CS、NQ A、TSIIA、CA), 50 min(AF、BT、GT、IG)	0.58, 1.05, 3.04, 2.49, 4.63, 0.08, 0.49, 1.09, 1.38, 2.22, and 23.1 mg/g	94.6%, 98.2%, 96.7%, 96.8%, 97.2%, 95.6%, 96.8%, 98.3%,	[113]

(*continued on next page*)

Table 2 (*continued*)

Analytes	Sample matrix	DESs composition(mole ratio)	Method of extraction	Yield	Recovery rate	Ref
	and *Salvia miltiorrhiza* roots				97.3%, 95.9%, and 98.7%	
Anthocyanins	saffron processing waste	L-lactic acid/glycine (5:1)	Liquid/solid: 60 mL/g, 50–60 °C, DESs concentration: 55% (w/v), 800 rpm,	Total polyphenols yield: 132.43 ± 10.63 mg gallic acid equivalents per g of dry mass		[82]
cyanidin-3-acetyl glucosamine, cyanidin-3-p-coumaryl glucoside, delphinidin-3-glucoside, delphinidin-3-p-coumaryl glucoside, malvidin-3-acetyl glucoside, malvidin-3-glucoside, malvidin-3-coumaryl glucoside, pet-3-acetyl glucoside, pet-3-coumaryl glucoside	*Myrothamnus flabellifolia*	Sucrose/citric acid/water (1:1:10)	Solid/liquid: 50:1, 50–55 °C, 90 min, 25% water(v/v)			[118]

1: Heat-assisted extraction; 2: Infrared extraction.

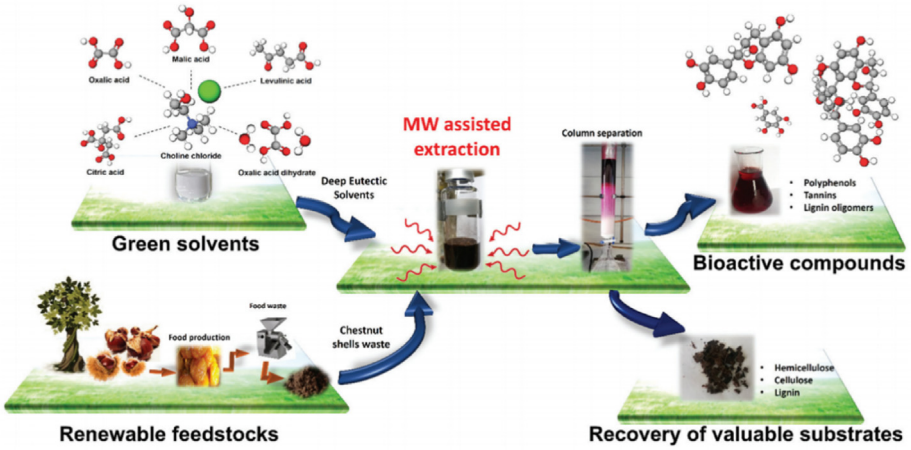

Fig. 4. Overview of the MWDA extraction process developed for polyphenol and lignocellulose residue isolation and recovery from CSW using different acid-based DESs (Reproduced with permission from Ref. [99]).

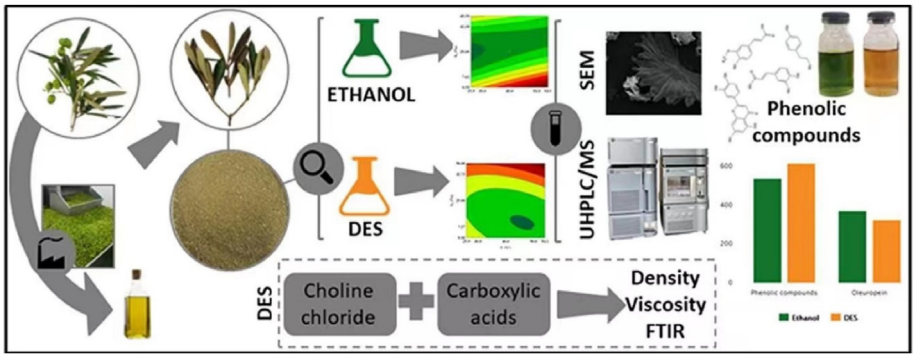

Fig. 5. Overview of the ChCl-based DESs as potential solvent for extraction of phenolic compounds from olive leaves and the comparison between ethanol (Reproduced with permission from Ref. [100]).

bonding acceptor. This may be due to the better water solubility of phenolics, which makes it easier to enter non-ionic DESs systems with multi hydroxyl structures.

3.3. Terpenoids

Terpenoids, which are comprised of five carbon isoprene units, have numerous functions, including anti-oxidant, antimicrobial, and antitumor properties [119,120]. A simple one-step extraction based on DESs ChCl and D-(+)-glucose (5:2) was investigated to extract volatile monoterpenes, and phenolic compounds from peppermint leaves. The method solved the issues caused by intermittent, time-consuming extraction techniques used to prepare two kinds of extracts simultaneously [97]. Optimization of DESs-

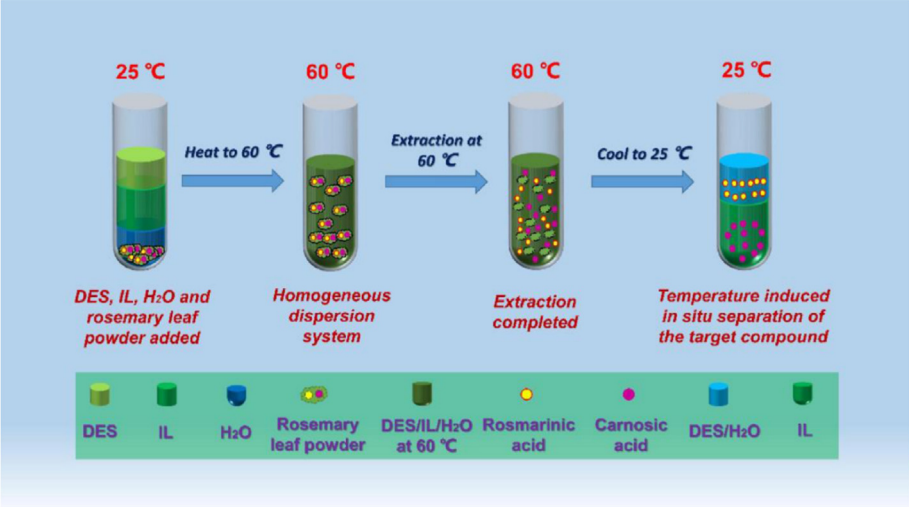

Fig. 6. The flow chart of the proposed thermo-switchable extraction method by using deep-eutectic solvent/ionic liquid/water mixture (Reproduced with permission from Ref. [106]).

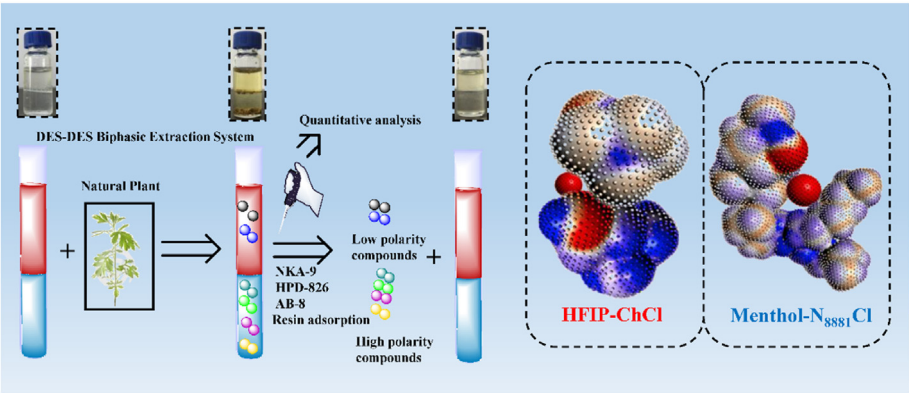

Fig. 7. Schematic diagram of the DESs-based biphasic extraction system for simultaneous extraction and separation of high and low polarity compounds from *Artemisia annua* Leaves(Reproduced with permission from Ref. [68]).

based extraction procedure has attracted considerable attention to improve the goal of eco-sustainable and cost-effective extraction, as shown in Table 3. The maximum yield of cynaropicrin was extracted from *Cynara cardunculus* L. leaves when the quaternary ammonium salt-based ionic DESs consisting of decanoic acid and $[N_{4444}]Cl$ with a 2:1 M ratio [121]. In addition, 11 ChCl-based NADESs systems were tested for the extraction of iridoids in *Lippia citriodora*. The ionic DESs consisting of ChCl/lactic acid (1:2) showed excellent extraction of iridoids compared to the conventional solvent(menthol). In optimizing the extraction conditions, the researchers investigated the effects of radiation intensity, water content, and temperature on the extraction amount of iridoids in the microwave-assisted process. The optimal conditions were 63.68 °C, 32.19% water in the extraction solvent, and 17.08 min microwave irradiation time [72]. In 2021, the adsorption/desorption features of carnosic acid and carnosol from the DESs ChCl:lactic acid (1:2) extract of Salvia officinalis on five macroporous resins were investigated. Under optimal conditions, the extraction efficiency of carnosic acid with three recycling steps decreased from 97.64% to 88.94% [104]. An ionic DESs, quaternary ammonium salts, was used to extract artemisinin and triterpenoid saponins from *Artemisia annua* leaves and the husks of *Xanthoceras sorbifolia* Bunge, resulting in excellent extraction efficiencies [122,123].

Furthermore, non-ionic DESs also showed excellent extractability of terpenoids [67,124,125]. For example, a simple preparation with menthol-based DESs was established for extracting taxanes from *Taxus chinensis* needles. Different parameters, such as the HBA to HBD mole ration, proportion of water in the extraction solvent, solid-liquid ratio, extraction time, and ultrasonic intensity, were assessed to obtain satisfactory extraction yield. The total extraction capacity of the main taxanes was increased by 25–44% compared to conventional methods [126].

3.4. Polysaccharides and glucosides

Polysaccharides are useful bioactive compounds with numerous activities. They are typically extracted using hot water, which demands considerable energy and time [38]. Some representative application has been indicated in Table 4. In the previous year, the ionic DESs composed of ChCl and 1,4-butanediol at a 1:4 ratio was discovered as the best ionic DESs for extracting polysaccharides from *Dioscorea opposite* Thunb with ultrasonic assistance. It yielded a higher extraction yield than the conventional method using hot water as an extraction solvent [127]. In addition, a study on thirty non-ionic DESs extracting and separating sugar from banana puree was conducted to identify new and eco-friendly solvents. As a

Table 3
The representative application of ionic and non-ionic DESs for extraction of terpenoids from natural herbal medicine.

Analytes	Sample matrix	DESs composition(mole ratio)	Method of extraction	Yield	Recovery rate	Ref
Terpenoids by ionic DESs						
Iridoids	*Lippia citriodora*	ChCl/lactic acid (1:2)	MAE, 63.68 °C, 17.08 min, 32.19% water (v/v)	9.69 mg/g		[72]
Anthocyanins, phenolic acids, flavonoids, other polar compounds	*Hibiscus sabdariffa* L.	ChCl/oxalic acid (1:1), 55% water	MAE, liquid/solid/: 1:30 mL/mg, 75 °C	10.43 ± 0.92, 24.41 ± 0.32, 6.00 ± 0.09, 44.25 ± 1.29 mg/g		[66]
Artemisinin	*Artemisia annua* leaves	methyl trioctyl ammonium chloride/1-butanol(N_{81}Cl-NBA) (1:4)	UAE (180 W), liquid/solid: 17.5:1, 45 °C, 70 min	7.9936 ± 0.0364 mg/g	85.65%	[122]
Cynaropicrin	*Cynara cardunculus* L. leaves	decanoic acid/[N_{4444}] Cl (2:1)	Solid/liquid: 1:30, 25 °C, 60 min, 70 wt % water, 1000 rpm		73.6 wt %	[121]
Triterpenoid saponins	Husks of *Xanthoceras sorbifolia* Bunge	tetrapropylammonium bromide/lactic acid (1:2)	Liquid/solid: 26 mL/g, 78 °C, 28 min, 35% water (v/v)	72.11 ± 0.61 mg Re/g dw	77.74%	[123]
Aucubin, geniposide, isoquercetin	*Eucommia ulmoides* Oliver leaves	ChCl/1,4-butanediol/Vc (1:1:0.2, mol/mol/mol), (Vc: ascorbic acid)	UAE, solid/liquid: 1:18.5 g/mL, 53 °C, 20 min, 20% water (v/v)	4.288, 0.330, 1.087 mg/g	78.75%, 70.36%, 77.26%	[88]
Carnosic acid	*Salvia officinalis*	ChCl:lactic acid (1:2), 10% (v/v) water	Solid/liquid: 50 mg/1 mL, 25 °C, 1500 rpm, adsorbed for 3 h, desorbed for 2 h		97.64 ± 0.03%	[104]
Artemisinin	*Artemisia annua* Leaves	HFIP/ChCl (1:1)-Menthol/N_{8881}Cl (2:1) biphasic system (1:1) (v/v)	Liquid/solid: 15/1, 20 °C, 30 min	6.21 mg/g	85.7%	[68]
Volatile monoterpenes	peppermint leaves (*Mentha piperita* L)	ChCl/D-(+)-glucose (5:2)	UAE, solid/liquid: 100 mg/mL, ambient temperature, 45 min			[97]
Aucubin, geniposidic acid, Asperuloside	*Eucommia ulmoides* leaves	ChCl/L-(+)-ascorbic acid (2:1)	MAE, liquid/solid: 25 mL/g, 75% water (v/v)	total content of iridoidsd:8.99 mg/g	94.91%, 96.09%, 95.16%	[70]
Terpenoids by non-ionic DESs						
Ursolic acid, oleanolic acid and betulinic acid	*Eucalyptus globulus* bark	Menthol/thymol (1:2)	Sample/solvent: 200 ± 3:3.00 ± 0.05 mg/g, room temperature, 4 h	ursolic acid: 93 ± 1 mg/g	1.8 wt %, 0.84 wt % and 0.30 wt %	[124]
Taxanes	*Taxus chinensis* needles	Menthol/1-propanol ratio 1:1	UAE (250 W), solid/liquid: 1:30 g/mL, 30 min, 80% water		90.26–109.00%	[126]
Artemisinin	*Artemisia annua*	L-carnitine/isosorbide (1:2)	UAE, solid/liquid: 50 mg/mL, 48 °C, 32.62 min	1.1954 mg/g		[125]
Oleuropein	Olive leaf	Glucose/fructose/water (GFW) (1:1:11)	UAE, solid/liquid: 20 mg/mL, 75 °C, 60 min	1630.80 mg kg^{-1} dw		[67]

result, four of them were selected Malic acid-based non-ionic DESs were the most suitable solvents for removing soluble sugars from banana puree using microwave-assisted extraction [36]. Moreover, the typical ionic DESs consisting of ChCl and polyol exhibited excellent extraction ability in extracting two glycosides (echinacoside and oleuropein) from *Syringa pubescens* Turcz. Compared to common organic solvents and other DESs, the recoveries of echinacoside and oleuropein extracted by the DESs achieved 80.04% and 86.21%, respectively [128]. Furthermore, Phaisan et al. used non-ionic DESs, called honey-based and some sugar-based non-ionic DESs, to extract, analyze, and bioconvert daidzin from *Pueraria candollei* var. *mirifica* (PM) root. The sugar-based non-ionic DESs (water:sucrose:glucose:fructose) was the most useful extraction solvent compared to H-NADESs, water, and ethanol; the daidzin concentration obtained was 75.8 μg/mL. Furthermore, honey glucosidase transformed daidzin to daidzein, indicating that honey glucosidase may improve the oestrogenic activity and bioavailability of PM phytochemicals [54]. A novel designer ChCl/glycerol and ultrasound pretreatment was developed to improve the digestibility of sugarcane bagasse. The combination yield (276.8 mg/g biomass) was higher than either of the individual pretreatments (ChCl/glycerol, 235.3 mg/g; ultrasound, 174.5 mg/g), which might help develop approaches for better biomass conversion [129]. Other ChCl-based DESs for extracting glycosides also possessed high extraction yields, reaching 14.97–55.11 mg/g [130–132].

Several studies on non-ionic DESs extracting polysaccharides and glucosides reported extraordinary extraction yields and recoveries. Cai et al. showed that ethanolamine-o-cresol (molar ratio 1:1) containing 50 wt % ET-OC was selected as the best extraction solvent for extracting polysaccharides from *Ganoderma lucidum*. In this study, nine temperature-responsive DESs (TRDESs) were synthesized to form a system that recovered polysaccharides into an aqueous phase after changing the temperature. The TRDESs could be recycled and reused [133]. From current reports, it can be seen that the extraction of polysaccharides and glucosides is mostly based on the ion state DESs based on ChCl as the HBA. The main reason may be that macromolecular carbohydrates are more likely to bond with the ion state HBA during the extraction process, while the multi hydroxyl structure in the non-ion state is more likely to compete with polysaccharides and glucosides, leading to a decrease in extraction efficiency. Therefore, there are not many reports on the use of non-ionic DESs for extracting polysaccharides and glucosides.

3.5. Alkaloids

The utilization of DESs in extracting alkaloids is extremely limited [109]. This study compared the prospects and efficiency of ionic DESs for extracting Amaryllidaceae alkaloids from *Crinum powellii* bulbs, a representative example of plant material, to common organic solvents (methanol, ethanol, and water). The extraction capacity of the DESs, ChCl:fructose (5:2) containing 35% H_2O, as a solvent was 2.43, 2.25, and 2.38 fold higher than that of ethanol, methanol, and water, respectively [37]. Wang et al.

Table 4
The representative application of ionic and non-ionic DESs for extraction of polysaccharides and glucosides from natural herbal medicine and other natural plants.

Analytes	Sample matrix	DESs composition (mole ratio)	Method of extraction	Yield	Recovery rate	Ref
Polysaccharides and glucosides by ionic DESs						
echinacoside and oleuropein	*Syringa pubescens* Turcz	ChCl/glycerol (1:2)	UAE and stirring heating methods (200 W), liquid/solid: 20:1 mL/g, 68 °C, 45 min, 20% water	3.06 ± 0.19, 0.46 ± 0.08 mg/g	80.04% and 86.21%	[128]
protodioscin, protogracillin, pseudoprotodioscin, and pseudoprotogracillin	*Dioscoreae Nipponicae* Rhizoma	ChCl and malonic acid (1:1)	UAE (300 W, 40 kHz), liquid/solid: 57.5 mL/g, room temperature, 23.5 min, 54% water		79.90%, 68.12%, 67.27%, and 74.8%	[134]
(2″-O-galactopyranosylorientin, orientin and vitexin	Flos Trollii	ChCl/zinc bromide (1:1)	Liquid/solid: 42 mL/g, 50 °C, 28 min, 48% water	total yield: 14.97 mg/g	80.5%, 78.2% and 75.4%	[130]
Flavonoids, iridoids, phenylpropanoids, and verbascoside	*Lippia citriodora*	ChCl/lactic acid (1:2)	MAE, 63.68 °C, 17.08 min, 32.19% water	Total phenolic yield:73.13; 6.28, 9.69, 14.87 and 12.52 mg/g		[72]
Chinese yam polysaccharides	*Dioscorea opposita* Thunb (Chinese yam)	ChCl/1,4-butanediol (1:4)	UAE, liquid/solid: 30 mL/g, 94 °C, 44.74 min, 32.89% water (v/v)		15.98 ± 0.15%	[127]
Glycyrrhizic Acid	*Glycyrrhiza glabra*	ChCl/lactic acid (1:1)	UAE, liquid/solid: 30:1 mL/g, 30 °C, 15 min, 30% water (v/v)	55.11 mg/g		[131]
Apigenin-7-O-glucoside, luteolin-7-O-glucoside, quercetin-3-O-glucoside	*Achillea millefolium* L	ChCl/lactic acid 1:2	UAE, solid/liquid: 500:10 mg/mL, 50 ± 1 °C, 30 min, 25%water (w/w)			[74]
Sugar	sugarcane bagasse	ChCl/glycerol (1:10)	UAE, solid/liquid: 0.6:20 g/g, 121 °C, 7.79 min, enzymatic saccharification,	312 mg/g biomass		[129]
Flavone di-C-glycosides	*Premna fulva* Craib	ChCl/1,3-propanediol (1:2)	UAE, liquid/solid: 31.00 mL/g, 43.00 min, 33.00% water	17.37 mg/g	81.59%	[132]
Soluble sugars	ripe banana	malic acid/beta-alanine/water (1:1:3)	MAE, sample/DESs:3:30 g/g, 25 °C, 30 min, 30% water (w/w)	106.9 g/100 g		[36]
Polysaccharides and glucosides by non-ionic DESs						
Polysaccharides	*Ganoderma lucidum*	Ethanolamine/o-cresol (1:1)	Liquid-solid ratio: 30:1, 60 °C, 50 min, 50 wt % ET-OC	92.35 mg/g	88.09%	[133]

reported a green extraction strategy for extracting bioactive compounds from tea leaves with only 20s, as shown in Fig. 8 [135]. Some studies used ionic DESs to extract caffeine from coffee with satisfactory results [136,137], as showed in Table 5.

Recently, studies on extracting alkaloids with non-ionic DESs have increased gradually. For example, harmine extracted from the seeds of *Penganum harmala* L. is recognized as a β-carboline alkaloid. Fan et al. reported excellent extraction efficiency of harmine using a non-ionic DESs of DL-menthol and anise alcohol (1:1). The non-ionic DESs recommended here can be reused by pH adjustment in the aqueous phase at least five times through back extraction [138]. In addition, 0.427 ± 0.018 and 2.362 ± 0.055 mg of boldine could be extracted from 1 g of the leaves of *Peumus boldus* using ChCl/lactic acid (ionic DESs) and proline/oxalic acid (non-ionic DESs), respectively. This efficiency is more effective than using common methanol and water [109]. Lactic acid/L-menthol (5:2) coupled with ultrasonic-assisted extraction had the highest tryptanthrin extraction yield from *Baphicacanthus cusia* leaves with 0.356 mg/g. The optimal temperature for this extraction was 60.5 °C because it could enhance solute solubility and diffusivity in non-ionic DESs. On the other hand, excessive temperatures (>75 °C) may alter the ultrasonic cavitation characteristics and mass transfer power [139]. The current findings examined the use of volatile non-ionic DESs for the efficient and environmentally friendly extraction

Fig. 8. A fast, highly efficient and ecofriendly using DESs for mechanochemical extraction (MCE) was developed to extract bioactive compounds from tea leaves. ((Reproduced with permission from Ref. [135]).

Table 5
The representative application of ionic and non-ionic DESs for extraction of alkaloids from natural herbal medicine.

Analytes	Sample matrix	DESs composition(mole ratio)	Method of extraction	Yield	Recovery rate	Ref
Alkaloids by ionic DESs						
Caffeine	green coffee beans	Glycerol/betaine (2:1)	60 °C, 3 h, 250 rpm, 10% water (v/v)	caffeine equivalents per 100 g of dry-weight GCB		[136]
Caffeine	Turkish coffee samples	ChCl/phenol (1:3)	Vortex extraction, sample/DESs:5:400 mL/μL, 5 min	LOD: 0.12 μg mL^{-1}	>92%	[137]
lycorine, crinine and crinamine	*Crinum powellii* bulbs	ChCl/fructose (5:2)	UAE, 50 °C, 1 h, 35% water	0.913, 0.167, 0.053 mg/ml		[37]
TBM, EGC, CAF, EC, EGCg, ECg and KAE	Tea leaves	ChCl/1,4-butanediol (1:3)	Solid/liquid: 50 mg/mL, 20s, 50 wt % water, MCE speed: 4 m/s	0.36, 32.65, 22.65, 7.18, 72.08, 12.39, 0.0035 mg/g		[135]
Alkaloids non-ionic DESs						
protopine, chelidonine, berberine, chelerythrine and coptisine	*Chelidonium majus*	Menthol/camphor and menthol/thymol mixtures	UAE, ambient temperature, 15 min		16%, 35%, 76%, 12%, 180%	[140]
Coclaurine, N-methylcoclaurine, laurolitsine, isoboldine, boldine, reticuline, isocorydine, laurotetanine, N-methyllaurotetanine	*Peumus boldus* leaves	L-proline/oxalic acid (1:1)	Solid/liquid: 10/1, room temperature, 20 min, 20%water			[33]
boldine	*Peumus boldus* leaves	l-Proline/Oxalic acid (1:1)	Heating + stirring extraction, solid/liquid: 5:1 mg/mL, 50 °C, 50 min, 20% water, 340 rpm	2.3615 mg of boldine per gram of plant		[109]
Harmine	The seeds of *Penganum harmala* L.	DL-menthol/anise alcohol (1:1)	Sample/DESs: 25:0.5 mL/mL, 25 °C, 5.0 min, 4% water (v/v), pH8.0		further purified as high as (97.5 ± 0.93) %	[138]
Tryptanthrin	*Baphicacanthus cusia* Leaves	lactic acid/L-menthol (5:2)	UAE, solid/liquid: 80.0 mL/g, 60.5 °C, 30 min	0.356 mg/g		[139]

of Chelidonium alkaloids from the *Chelidonium majus* plant. Compared to the extraction with acidified methanol, menthol-camphor and menthol-thymol mixtures yielded higher amounts of alkaloids and higher wetting dynamics to water. The non-ionic DESs could be employed to extract Chelidonium alkaloids effectively and sustainably [140].

3.6. Miscellaneous

3.6.1. Phenylpropanoids

Several studies have been conducted to determine the extraction efficiency of ionic DESs for phenylpropanoids [141], as showed in Table 6. For example, Ivanović et al. reported that the ionic DESs of ChCl-lactic acid had the maximum extraction efficiencies for phenylpropanoids from *Lippia citriodora* compared to other presented ChCl-based DESs and methanol [72]. In addition, Tang et al. developed a biphasic system for the simultaneous extraction and separation of high-polarity compounds via the simple extraction of chlorogenic acid from *Artemisia annua* leaves. The DESs used in that study were a hydrophilic DESs phase (hexafluoroisopropanol-ChCl: HFIP-ChCl) and a hydrophobic DESs phase (Menthol-tricaprylylmethylammonium chloride: Menthol-N_{8881}Cl). Chlorogenic acid (7.89 mg/g) was extracted and moved to the bottom layer (HFIP-ChCl with 1:1 mol ratio) from *Artemisia annua* leaves. This method was resource efficient, faster, and more efficient than traditional extraction methods for extracting bioactive compounds with varying polarities [68]. In addition, a ternary system-assisted microwave extraction was first investigated for the extraction of chlorogenic acid in *Eucommia ulmoides* Oliver leaves, in which tiny ascorbic acid (AA) was added to modify the acidity of the binary DESs. The ionic DESs with ChCl, 1,4-butanediol and AA with a mole ratio of 1:1:0.2 possessed excellent extractability for compounds. The extraction system that relies on tailor-made TDESs was commercially efficient and productive for extracting more valuable products from plants because of its superior recovery and antioxidant activity [88]. Similarly, Yue et al. used the proline-malic acid, a non-ionic DESs, to extract phenolic acids from chlorogenic acid (CGA) from Artemisiae Scopariae Herba, which integrated an ultrasonic technique. An excellent extraction capacity with a yield of 28.23 mg/g was obtained under the optimal conditions: 15% water (wt.) with the proposed DESs, 1.0/10 (g/mL) solid-liquid ratio, 300 W ultrasonic power, and 25 min extraction time. The DESs was stable and antioxidant activity could be analyzed better than in water and ethanol [142].

3.6.2. Pigments

DESs have potential applications for pigments extraction (Table 7). For example, Sakti et al. used a ChCl-glycerol DESs to extract brazilin (a red pigment) from the traditional Chinese medicine *Indonesian cassia* and sappan wood, which has been used as an ingredient of flavor and drugs. The Gycerol-ChCl (1:2) DESs produced a high level of brazilin extraction (368.67 μg/ml), exceeding those obtained using a conventional extraction method by many times [49]. In another study, non-ionic DESs called NADESs, consisting of organic acids and sugars, were used to extract curcuminoid pigments from *Curcuma longa* L. The antioxidant activities and stabilities in different non-ionic DESs were investigated. The optimal method of extracting pigments was a citric acid-glucose NADESs (ratio 1:1) at 50 °C, 1% water, 0.1 g/10 mL solid-liquid ratio, and 30 min. A similar study reported the enhanced stability of red and violet betalains from beetroot (*Beta vulgaris*) waste extracted using DESs magnesium chloride hexahydrate [$MgCl_2 \cdot 6H_2O$]:urea (2:1) adjusting pH to 3 with HCl [143].

Non-ionic DESs also show high extraction yields and recoveries. According to one study, non-ionic DESs-based ultrasound-assisted extraction could be an effective application strategic approach for extracting bioactive compounds from *Baphicacanthus cusia* leaves. High yields of indigo and indirubin of 1.744 and 0.562 mg/g, respectively, were obtained under the optimal extraction conditions: 5:2 (mol/mol) lactic acid/L-menthol ratio, 80.0 mL/g solid-

Table 6
The representative application of ionic and non-ionic DESs for extraction of phenylpropanoids from natural herbal medicine.

Analytes	Sample matrix	DESs composition(mole ratio)	Method of extraction	Yield	Recovery rate	Ref
Phenylpropanoids by ionic DESs						
Aesculin, fraxin, aesculetin and fraxetin	*Cortex Fraxini*	betaine/glycerin (1:3)	UAE, solid/liquid: 15 mg/mL, 30 min, 20%water (v/v)	36.26, 30.14, 1.87, and 9.98 mg/g	89.23%, 93.42%, 95.71% and 85.23%	[141]
Phenylpropanoids	*Lippia citriodora*	ChCl/lactic acid (1:2)	MAE, 63.68 °C, 17.08 min, 32.19% water	17.23 mg/g		[72]
Coumarin	*Indonesian cassia* barks (Cinnamomum burmannii Blume)	Gycerol/ChCl 1:2 (w/w)	UAE, powder/DESs: 1:8 (w/w), 30min, 20% water	920.43 μg/ml		[49]
Chlorogenic acid	*Eucommia ulmoides* Oliver leaves	ChCl/1,4-butanediol/Vc (1:1:0.2, mol/mol/mol), (Vc: ascorbic acid)	MAE, solid/liquid: 1:18.5 g/mL, 20 min, 53 °C, 20% water	3.659 mg/g	70.36%	[88]
Chlorogenic acid	*Artemisia annua* leaves	HFIP-ChCl (1:1)/Menthol-N_{8881}Cl (2:1) biphasic system (1:1) (v/v)	Liquid/solid: 15/1, 20 °C, 30 min	7.89 (transferred to the lower layer (HFIP-ChCl with 1:1 mol ratio))	91.8%	[68]
Phenylpropanoids by non-ionic DESs						
Caffeoylmalic acid, psoralic acid-glucoside, rutin, psoralen and bergapten	Fig (*Ficus carica* L.) leaves	Glycerol/xylitol/D-(−)-Fructose (3:3:3)	MAE, liquid/solid: 17.53, 64.46 °C, 24.43 min	6.482, 16.34, 5.207, 15.22, and 2.475 mg/g	79.2%, 83.4%, 85.5%, 81.2% and 75.3%	[114]
Chlorogenic acid	Artemisiae Scopariae Herba	Proline/malic acid (1:1)	UAE (300 W), solid/liquid: 1:10 g/mL, 25 min, 15% (wt) water	28.23 mg/g		[142]

liquid ratio, and 60.5 °C extraction temperature [139]. Liu et al. reported that the proposed method was an effective option for natural pigment extraction because it is eco-sustainable [45]. Moreover, 22 different NADESs were screened and applied to extract pigments (hydroxysafflor yellow A and anhydrosafflor yellow B) from safflower. The results showed that the total maximum extraction yields of the five main flavonoids reached 20.820 mg/g using a DESs composed of L-proline-acetamide. The hydroxysafflor yellow A and anhydrosafflor yellow B yields were 32.83 and 8.80 mg/g, which were 22.8% and 53.0% higher than that of water, respectively [81]. In 2021, a series of hydrophobic non-ionic DESs based on fatty acids were developed to obtain optimal extraction efficiency of β-carotene and improve the stability of extracted carotenoids from pumpkin. Non-ionic DESs consisting of C8 and C10 fatty acids were chosen to optimize the extraction process, along with ultrasound-assisted extraction. The optimal extraction conditions yielded the highest carotene content of 151.41 g/mL. The extracted carotenoids in the optimal non-ionic DESs extract showed high stability over a 180-day storage period [55].

3.6.3. Anthraquinones

Recently, the HFIP-based DESs (HFIP-DESs) can establish ATPS with different mineral salts and have a considerably higher phase separation ability than small molecule aliphatic alcohols, HFIP, and traditional DESs. ATPSs based on HFIP-DESs were first used to extract anthraquinones (AQs) from samples of Rhei Radixet Rhizoma. More than 92% of AQs (including aloe-emodin, rhein, emodin, chrysophanol, and physcion) were enhanced in the DESs phase of the ATPS consisting of ChCl-HFIP DESs and Na_2SO_4. The ATPS extraction method achieved high extraction efficiency but consumed only 0.5 mL of organic solvent (HFIP) compared to the conventional chloroform extraction method (60 mL chloroform consumption) [43]. Furthermore, novel non-ionic DESs was proposed using natural long-chain alkanol and alkyl carboxylic acid. The total yield of anthraquinone using DESs C_{14} alcohol-10-undecenoic Acid (1:4), 10% HCl was 21.52 mg/g. The extraction yield was comparable to the Chinese pharmacopoeia method (21.22 mg/g) and significantly higher than other disclosed ionic DESs-based extraction methods [50].

3.6.4. Other compounds

Some studies on DESs-based extraction methods applied to other compounds, such as lipids, steroids and protein (Table 8). Cai et al. investigated lipid extraction from *Nannochloropsis* sp. using a three-phase partitioning model,as shown in Fig. 9. The specific method used CO_2 as the controller for the properties of the DESs extraction phase and realized the separation of lipids by blowing CO_2 and N_2 in and out intermittently. In the above method, the optimal conditions to achieve the maximum extraction rate were selected as follows: the mass fraction of ammonium sulfate, liquid-solid ratio, textraction temperature, and the extraction time were 20%, 35:1, 80 °C and 90 min, respectively. The extraction efficiency of this method was much higher than that of the t-butanol-based TPP system (135 mg/g) [144]. In the extraction of vitamin D from button mushrooms, ionic DESs glycerol and ChCl (3:1), along with ultrasonication showed high efficiency. The amount of vitamin D_2 observed after 48 h of UV-C exposure was 364.2 ± 2.60 μg/g DW. This amount was approximately three times the maximum amount by liquid−liquid extraction according to previous studies [145]. In another study on menthol-based DESs, Khare et al. reported that menthol-pyruvic acid (1:2) achieved a maximum extraction yield and retained extraction efficiency (up to 28%). The ergosterol was exposed to UV radiation for conversion to ergocalciferol (vitamin D_2) with an yield of ergocalciferol yield equivalent to 2142.01 μg/g dry weight of mushroom, which was much higher than the DESs-based extraction method reported previously [146]. A new method for the synergistic extraction of pumpkin seed protein was developed using a polyethylene glycol (PEG200)-based DESs aqueous solution and ultrasonic-microwave to avoid the denaturation of pumpkin seed protein in organic solvents. Furthermore, the entire extraction process, including protein precipitation, took only 4 min, offering an effective method for the rapid and effective extraction of pumpkin seed protein [147]. Two ChCl-based DESs extracted antioxidants from *Polygonum maritimum* L., *Polygonum aviculare* leaves with ultrasonication assistance, showing good extraction yields [148,149]. A non-ionic DESs (lactic acid-glucose) coupled with microwave-assisted extraction also proved the potential extractability for antioxidants [150]. According to Stupar et al., fatty acid-based NADESs were better solvents for carotenoids extraction than DL-menthol-based NADESs, despite DL-menthol-

Table 7
The representative application of ionic and non-ionic DESs for extraction of pigments from natural herbal medicine.

Analytes	Sample matrix	DESs composition(mole ratio)	Method of extraction	Yield	Recovery rate	Ref
Pigments by ionic DESs						
Anthocyanins	*Nitraria tangutorun* Bobr. fruit	ChCl/1,2-propanediol	UAE, solid/liquid: 1:15 g/mL, 50 °C, 30 min, 25% water (w/w)	1.413 ± 0.054 mg/g	>95%	[108]
Anthocyanins	fresh mulberry	ChCl/citric acid/glucose (1:1:1)	Liquid/solid: 22 mL/g, 45 °C, 30 min, 30% water (v/v), extraction two times	6.05 mg/g (fresh weight)		[107]
Anthocyanins, phenolic acids, flavonoids, other polar compounds	*Hibiscus sabdariffa* L.	ChCl/oxalic acid (1:1)	MAE, liquid/solid: 1:30 mL/mg, 75 °C, 55% water	10.43 ± 0.92, 24.41 ± 0.32, 6.00 ± 0.09, 44.25 ± 1.29 mg/g		[66]
Betalains	Beetroot (*Beta vulgaris*) waste	magnesium chloride hexahydrate [MgCl2·6H2O]:urea (2:1), pH3(HCl)	UAE, solid/liquid: 1:30 g/mL, 25 °C, 3 h	3.99 ± 0.26 mg/g	83.75 ± 12%	[143]
15 anthocyanins	*Lycium ruthenicum* Murr. fruit	ChCl/1,2-propanediol (1:2)	Liquid/solid: 20:1, 52 °C, 45 min, 10% water (v/v)	4.45 ± 0.07 mg/g	>95%	[44]
Brazilin	*Caesalpinia sappan* heartwoods	Gycerol/ChCl (1:2) (w/w)	UAE, powder/DESs:2:1 (w/w), 30min, 47.57% water	373.28 μg/ml		[49]
Anthocyanidins	*Artemisia annua* Leaves	HFIP-ChCl (1:1)/Menthol-N_{8881}Cl (2:1) biphasic system (1:1) (v/v)	Liquid/solid: 15/1, 20 °C, 30 min	8.9 mg/g (transferred to the lower layer (HFIP-ChCl with 1:1 mol ratio))	88.1%	[68]
Pigments by non-ionic DESs						
Hydroxysafflor yellow A, anhydrosafflor yellow B	*Carthamus tinctorius* L.	L-Proline/Acetamide/water (1:1:2)	UAE (200 W), solid/liquid: 200 mg/mL, 50 °C, 30 min	32.83, 8.80 mg/g	88.5−107.7%	[81]
β-carotene	pumpkin	C8/C10 fatty acids (3:1)	UAE, solid/liquid: 7 mL/g,50 °C, 10 min	151.41 μg/mL	90%	[55]
Indigo and indirubin	*Baphicacanthus cusia* Leaves	Lactic acid/L-menthol (5: 2)	UAE, solid/liquid: 80.0 mL/g, 60.5 °C, 30 min	1.744 and 0.562 mg/g		[139]
Curcuminoids (BDMC, DMC, CUR)	*Curcuma longa* L.	Citric acid/glucose (1:1)	Solid/liquid: 0.1:10 g/mL,50 °C, 30 min, 15% water	16.54, 15.12, and 21.18 mg/g	BDMC (88.5%), DMC (94.4%), and CUR (93.2%)	[45]
Anthocyanins	saffron processing waste	L-lactic acid/glycine (5:1)	Liquid/solid: 60 mL/g, 50−60 °C, DESs concentration: 55% (w/v), 800 rpm	Total polyphenols yield: 132.43 ± 10.63 mg gallic acid equivalents per g of dry mass		[82]
cyanidin-3-acetyl glucosamine, cyanidin-3-p-coumaryl glucoside, delphinidin-3-glucoside, delphinidin-3-p-coumaryl glucoside, malvidin-3-acetyl glucoside, malvidin-3-glucoside, malvidin-3-coumaryl glucoside, pet-3-acetyl glucoside, pet-3-coumaryl glucoside	*Myrothamnus flabellifolia*	Sucrose/citric acid/water (1:1:10)	Solid/liquid: 50/1, 50−55 °C, 90 min, 25% water			[118]

based NADESs had already been thought an excellent solvent for extraction of carotenoids [55]. Moreover, ionic and non-ionic DESs have many applications as extracting solvents for other compounds, such as xanthones [151], inorganic elements [152,153], and organic phosphorus compounds [154].

4. Target recovery from the ionic and non-ionic DESs extraction solution

The recovering of extracted compounds is difficult owing to the low vapor pressure of DESs. On the other hand, several approaches, such as macroporous resins, liquid-liquid extraction, solid-liquid extraction, supercritical carbon dioxide, recrystallization, adsorption chromatography, and anti-solvents can be used to recover the targeted extracts from DESs [63,122,132]. Vacuum evaporation was used with the addition of water to isolate the curcuminoids from the crude extracts. This process induced the precipitation of curcuminoids from the crude cyrene and DESs extracts [101]. In another study, the addition of water or a weak base, such as NH_4OH, to the extract resulted in the formation of two phases due to the various polarities of the mixtures or the altered pH of the extract, which induced a change in the polarity of the NADESs extract. Eventually, both polar and non-polar compounds could be extracted and separated sequentially [55]. Huang et al. evaluated the recovery of rutin from ChGly. Water was the most efficient anti-solvent among tested solvents, with a recovery of 95.1%. After separation, water was evaporated by heating the ChGly solution under a vacuum, and the regenerated ChGly was then reused for rutin extraction [87].

Furthermore, the resin adsorption method is a straightforward and efficient method for recovering some bioactive compounds from DESs extraction solutions and reusing DESs [63]. Five macroporous resins, for instance (NKA-9, NKA-II, HPD-100, D101, and AB-8) were evaluated for their ability to recover the primary

Table 8
The representative application of ionic and non-ionic DESs for extraction of other compounds.

Analytes	Sample matrix	DESs composition(mole ratio)	Method of extraction	Yield	Recovery rate	Ref
Other compounds by ionic DESs						
Antioxidants	*Polygonum maritimum* L. (sea knotgrass)	ChCl/sucrose (1:2); ChCl/fructose (1:2)	UAE, solid/liquid: 1:40 (w/v), room temperature, 30 min, 30–40% water	25 mg of initial dry plant biomass/mL		[148]
Gallic Acid, 5-caffeoylquinic acid, myricitrin, 3′′-O-galloyl, Myricitrin, 3-chlorogenic acid, quercitrin, avicularin	*Polygonum aviculare* leaves	ChCl/levulinic acid (1:2)	UAE, liquid/solid: 85:1, 60 min, 70 °C, 38% water	39.80 mg/g DW, 11.83 mg/g DW, 10.47 mg/g DW, 7.91 mg/g DW, 7.16 mg/g DW, 4.26 mg/g DW, 3.02 mg/g DW		[149]
Steroid						
Ergosterol	Button Mushroom (*Agaricus bisporus*)	glycerol/ChCl (3:1)	UAE, solid/liquid: 1:20 g/mL	12 ± 3.04 μg/g of DW		[145]
Protein						
Pumpkin Seed Protein	Pumpkin (*Cucurbita moschata*) Seed Protein	PEG 200/ChCl (3:1)	UAE-MAE (140 W), solid/liquid: 28 g/mL, 43 °C, 4min, 28% DESs (w/w)		93.95 ± 0.23%	[147]
Inorganic elements						
Cobalt	Tomato sauce, green and black tea, and dark chocolate	n-phenyliminodiacetic acid/ChCl (2:1)	UAE, 40 °C, 4 min	LOD: 5.23 μg L^{-1} and LOQ: 17.67 μg L^{-1}	94.0–105.0%	[152]
Organichosphorus						
Chlorpyrifos	Cucumber samples	ChCl/acetic acid/4-chlorophenol	Agitated Acetonitrile (3.5 mL), cucumber, and pesticides (200 ng g^{-1}, each pesticide) into a homogenous solution (1 min), then cooled down with liquid nitrogen (10s), removed 2 mL ACN, then mixed frozen acetonitrile aqueous phase with ternary DESs, added 5 mL deionized water	LODs: 0.42–0.88 ng g^{-1} and LOQs: 1.5–2.9 ng g^{-1}	85–111%	[154]
Aldehyde						
Trans-cinnamaldehyde	*Indonesian cassia* barks (*Cinnamomum burmannii* Blume)	Gycerol/ChCl (1:2) (w/w)	UAE, solid/liquid:1:8 (w/w), 30 min, 20% water	1907.32 μg/ml		[49]
Xanthones						
α-mangostin	Mangostee (*Garcinia mangostana* L.)	ChCl/1,2-propanediol (1:3)	Solid/liquid: 1:10, room temperature, 4 h,		2.40–2.63%	[151]
Lipid						
Free fatty acid	Red Palm Biodiesel	K_2CO_3/glycerol (1:5)	Solvent/DESs: 1:3.5, 3 h, 300 rpm, settling time: 2 h			[52]
Lipid	*Nannochloropsis* sp.	Tetramethylguanidine/menthol (3:1)	liquid–solid ratio of 35:1, 80 °C,90 min, 20 wt % ammonium sulfate	172 mg/g		[144]
Other compounds by non-ionic DESs						
antioxidant	*Osmanthus fragrans* (Lour) flower	lactic acid/glucose (5:1)	MAE (497.12 W), solid/liquid: 31.14 mL/g, 60 °C, 2 h	101.81 mg Trolox equivalent/g		[150]
steroid						
ergosterol	mushroom	Menthol/pyruvic acid (1:2)	Solid/liquid: 1:20 g/mL, stirred for 2 h and then sonicated for 45 min	6995.00 μg ergosterol/g dry weight	28%	[146]
Coumarin						
psoralen and bergapten	Fig (*Ficus carica* L.) leaves	Glycerol/xylitol/D-(−)-Fructose (3:3:3)	MAE, liquid/solid: 17.53, 64.46 °C, 24.43 min	15.22, and 2.475 mg/g	81.2% and 75.3%	[114]
Inorganic elements						
As, Cd, Pb	Forage grass *Brachiaria brizantha* cv. Marandu	As, Cd: citric acid/malic acid/Water; Pb: malic acid/xylitol/water	As, Cd: UAE (40 kHz), solid/liquid: 90:9 mg/mL, 45 min; Pb: MAE, solid/liquid: 90:9 mg/mL, 10 min ramp up to 190 °C, then holding at 190 °C	As: 3.80 ± 0.20 mg kg^{-1}; Cd: 31.1 ± 0.1 mg kg^{-1}; Pb: 5.1 ± 0.3 mg kg^{-1}	80–120%	[153]
Pb,V	Peach leaves	Pb: malic acid/xylitol/water; V: citric acid/malic acid/water.	MAE, solid/liquid: 90:9 mg/mL, 10 min ramp up to 190 °C, then holding at 190 °C for 40 min, and cooled to 50 °C in 10 min.	Pb:1.18 ± 0.02 (μg g−1); V: 0.44 ± 0.01 μg g^{-1}	80–120%	[153]

bioactive compounds from an innovative ternary DESs extraction solution. The author reported that HPD-100 would be the most effective macroporous resin for recovering the target iridoids and phenolic acids. The author then ran five cycles to ensure the reuse performance of the new DESs solvent [88]. In another study, after extracting artemisinin from A. *annua* leaves and optimizing the resin amount, AB-8 could attain a considerably high adsorption yield of 85.65% among the six macroporous resins. Hence,

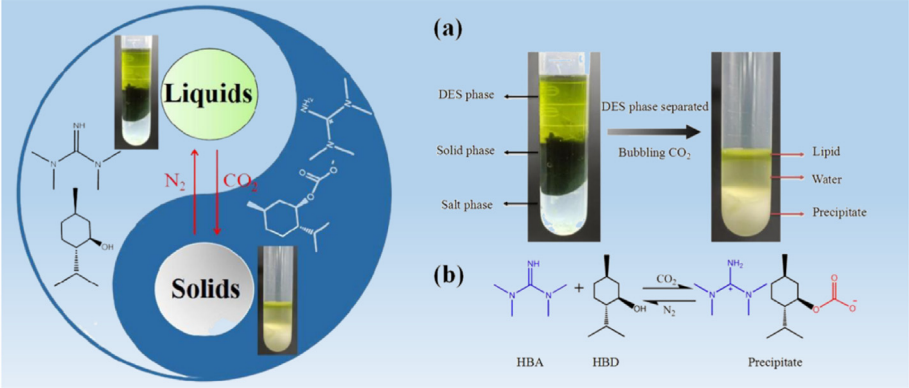

Fig. 9. (a) The lipid extraction process by using TPP and (b) the response characteristics of DESs by bubbling CO_2 and N_2. ((Reproduced with permission from Ref. [144]).

macroporous resin might be a simpler method for recycling DESs [122]. In a related study, dried and pretreated resin (80 g) and CGA crude extracts (20 mL diluted to 100 mL) were merged in a flask and agitated at room temperature for 24 h until an adsorption equilibrium state was reached to regain chlorogenic acid (CGA) [142]. In addition, the recovery of five insoluble or slightly soluble target compounds in a water-soluble DESs extraction solution was conveniently, easily, and efficiently achieved using macroporous resin D101 [114].

Cai et al. investigated the recovery of lipids after extraction from *Nannochloropsis* sp. Through three-phase partitioning based on CO_2-responsive DESs. The DESs solution could be separated from lipids and easily recycled by bubbling CO_2 and N_2 after extraction [144]. The target compounds can be successfully separated from DESs to achieve DESs cyclic utilization.

5. Factors influencing the extraction capacity of DESs

The physical and chemical properties of DESs, such as hydrogen bonding interactions, density, melting point, conductivity, polarity, pH, and viscosity, significantly impact their extraction capacity [63,85]. The physicochemical properties of the solvent are related directly to the extraction efficiency of the target compounds and have the potential to influence the extraction efficiency [55]. Optimizing the DESs based on these properties should allow for more effective extraction of target compounds from natural herbal medicine [85]. Screening the optimal DESs for extraction is the first step of optimization because different types of DESs show different abilities to extract diverse bioactive compounds. For example, less viscous or acidic-based DESs (ChCl-Lev and Pro-Lev) outperformed the other DESs in terms of the phenolic/flavonoid extraction efficiency [149]. The composition of DESs also determines their physicochemical properties and strongly influences the extraction efficiency of natural compounds. The slow mass transfer resulting from the high viscosity among most DESs at room temperature was overcome by increasing the extraction temperature and adding a specific amount of water to decrease the viscosity [130]. According to one study, less viscous ionic DESs (ChCl-ZnCl and ChCl-ZnBr) had higher extraction efficiency for flavone-C-glycosides than the other ionic DESs (ChCl-Ma and ChCl-Pa). The high extractability of flavone-C-glycosides with DESs is likely due to H-bonding interactions between the DESs and flavone-C-glycosides, and also DESs polarity [130]. Moreover, the suitable molar ratio of DESs is critical. During the extraction process, the acceptable molar ratio is linked directly to the melting point and temperature range. A Gly-La ratio of 1:1 was developed to enhance flavonoid extraction efficiency by Gly-La-based DESs because a partially acidic environment is helpful for flavonoid extraction and the extraction efficiency increases with decreasing HBA-HBD ratio. Extreme acid or alkali, however, will result in significant changes in the physicochemical properties of DESs, such as pH, polarity, viscosity, and density, which can reduce extraction efficiency [85]. Moreover, adding of water altered the viscosity of the non-ionic DESs, affecting the mass transfer rate and the extraction capacity. Furthermore, because water is a polar solvent, it enhances the polarity of the DESs, promoting the extraction of polar compounds [67]. Some studies also used acids and bases in a proper concentration or other solvents to simultaneously change the polarity and viscosity of DESs and extract more biocompounds from natural materials. For example, ammonium sulfate was chosen as the optimal salt in TPP because of its low solubility and suitable ionic strength for protein precipitation by salting out effect [144]. The extraction yield of polysaccharides shows a downward trend with increasing ET-OC concentration because of the increased viscosity of the TRDESs-water solution [133]. A recent study assessed the impact of NaCl addition on the recovery of bisphenols and discovered that the amount of NaCl can actually influence analytes diffusion between the sample solution and extraction solvent, lowering the solubility of the analytes in the sample solution and increasing extraction efficiency. The recoveries of bisphenols declined slightly as the salt addition was increased from 1.0 to 2.0 g. Nevertheless, too much salt increased the viscosity of the solution, causing partitioning and the diffusion rate of the analytes to decline [155].

External factors, including extraction temperature, pH, extraction time, liquid-to-solid ratio, and integration of other methods, such as ultrasonication, microwave-assisted method, stirring, and vortex, are of great importance for the extraction capacity of DESs. In terms of the extraction temperature effect on the mass transfer and thus the chemical composition, Hao et al. showed that the total flavonoids extracted increased from 35 to 55 °C and then decreased from 55 to 75 °C, indicating that temperature decreased the viscosity of DESs, but an excessive temperature might cause the dissolution of the total flavonoids [73]. In addition, the pH of the extraction solvents determines the degree of ionization and speciation of the analytes, which cause in a different distribution coefficient [156]. For example, the best extraction recoveries of bisphenols were achieved when the analytes were ionized at pH4 [155]. Microwave extraction and ultrasonic extraction, as auxiliary extraction techniques, play important roles as key optimization factors in increasing the extraction efficiency of active components of natural herbal medicine such as flavonoids, phenols, alkaloids, and polysaccharides. According to the data presented in this review, there is no specific pattern. In Tables 1–8 of this review, we

present in detail the selected auxiliary technologies, and also describe in detail the differences in yield between ultrasonic extraction and microwave extraction in the above. To our knowledge, the difference between microwave and ultrasound is mainly reflected in the difference in energy and its impact on the viscosity of DESs. More research is needed to report on the specific patterns.

Furthermore, the liquid-to-solid ratio influences the viscosity of DESs and mass transfer [73]. The hydrogen-bond interaction between DESs and extracts is significant [144]. As a result, obtaining the optimal liquid/solid ratio for lower viscosity of DESs, relatively weak hydrogen-bond interaction, and less waste of extractants is important. The extraction time is another significant parameter for the extraction of natural products [73]. The extraction yield improved when the extraction time was increased and reached a plateau after a certain time. Furthermore, the ultrasonic power and microwave parameters influence the extraction efficiency of DESs when coupled with ultrasound-assisted extraction or microwave-assisted extraction. The outcomes depend on the properties of target compounds to adjust these parameters. For example, recoveries lower than 80% for multiple metal ions in peach leaves were achieved when the DESs was combined with UAE. On the other hand, the extraction of V required a more aggressive method, such as MAE, when strongly bound to the components of the plant tissue [153]. In addition, the recommended particle size of the natural samples was 0.4–0.8 mm [157].

DESs in both ionic and non-ionic states have demonstrated excellent extraction capabilities for flavonoid components. However, most non-ionic DESs are added with a certain proportion of water during the extraction process to dilute the viscosity of the DESs extraction phase. Although the increase in water can save solvent costs to some extent, the extraction ability of ionic DESs is superior to that of non-ionic DESs in terms of flavonoid extraction ability. For the extraction process of phenolic compounds, a certain proportion of water is supplemented in most ionic DESs. However, there are not many non-ionic DESs that are used to extract classified compounds and choose to supplement the water, indicating that these non-ionic DESs have stronger extraction ability for phenolic compounds. This indicates that the presence of the water is not solely aimed at reducing the viscosity of DESs. Water as another auxiliary HBD has a special impact on enhancing the extraction ability of different components.

6. Evaluation of toxicity and biodegradability of DESs

DESs are being applied increasingly to various natural matrices. Hence, the safety and toxicology of these solvents have attracted attention [158–163]. The tunability of HBA and HBD allows for the facile synthesis of diverse types of DESs. On the other hand, DESs are not typically evaluated for their toxicity. Assessing the harmfulness of DESs is an important part of translating this new kind of solvent into useable extraction methods. The toxicological properties of ionic DESs and non-ionic DESs are not distinguished when conducting in vivo and in vitro toxicity experiments for DESs. For ionic DESs, the toxicity assessment of their quaternary ammonium salts is a crucial indicator. The ionic DESs need to be assessed because the toxicity values are different from the most toxic quaternary ammonium salts because of the synergies by the HBD. As the main branch of non-ionic DESs, NADESs show high bioavailability based on NADESs plant active extracts. Hence, non-ionic DESs are a powerful tool for developing functional food, nutritional health products and pharmacological agents [164–168]. Gutiérrez et al. [169]. reported an arginine-based therapeutic DESs as a solubilizing carrier of lidocaine. In this system, the intermolecular forces between lidocaine and the hydrogen bond acceptor and hydrogen bond donor of DESs were analyzed, including the type and strength of intermolecular and intramolecular bonds.

Although most DESs are composed of natural components, exhibiting advantages of higher safety, lower toxicity and cheaper cost than traditional organic solvents, research on toxicity, cytotoxicity, antimicrobial, antioxidative and anti-inflammatory evaluation is still needed. Those extractants obtained are usually used as ingredients in medicines and food, which makes the safety of DESs a vital issue. The biological activity of solvents can be evaluated using in vitro and in vivo assays, such as antimicrobial activity and toxicity toward animals and cells.

ChCl-based DESs are considered as green solvents because of the safety and biodegradability of ChCl. Pan et al. used a colorimetric MTT assay to assess the cytotoxicity of the DESs. They reported that the four ChCl-based and L-carnitine-based DESs had no toxicity on cells and had good biocompatibility [125]. The amino acid-based-DESs also showed no major health hazards and improved bioavailability owing to the increased solubility of the extracts [170]. Some studies indicated that NADESs are excellent alternatives to expensive organic solvents, and help improve the pharmacological effects [81]. In addition, a rat assay first reported that the NADESs-based extracts are biocompatible and do not require solvent removal before use [171]. Furthermore, the NADESs system appears to have a high selectivity index to be cytotoxic towards cancer cells without harming normal intestinal cells [172]. Similar anti-inflammatory activity could be achieved using DESs or traditional solvents, but DESs have superior advantages over organic solvents [73]. In addition, NADESs are generally less toxic than DESs. Moreover, the significant role of HBDs on cytotoxic profiles of NADESs was emphasized [32]. Nevertheless, further research on the toxicity of DESs is required for better development [48,73,81,101,136,170,172–174].

7. Remarks and prospects

At present, significant efforts are still needed to find new DESs applications, which will further lead to their continuous expansion. Based on this, classifying DESs can effectively select suitable types of DESs for new application fields. This review summarizes the differences between ionic and non-ionic DESs in the field of extraction technology for active components of natural herbal medicines. The classification of DESs based on whether it contains ion type components provides guidance for extracting active components with different structures. Future studies on the hotspots of DESs may focus on the following areas. (I) DESs need to be defined using the basic physical and chemical properties to discriminate between true “deep eutectic” and merely “eutectics” and reach consensus in the academic community. (II) The long stability of ionic and non-ionic DESs during prolonged use need to be determined. (III) Their toxicity and biodegradability require further study. (IV) The most crucial technical barrier related to the entire DESs field is the recovery of applied DESs, which is a very challenging field. This problem must be solved to ensure that DESs has a scientific and industrial future. Currently, a recovery method under study is back extraction, but whether it is the best recovery method remains to be determined. Most likely, new recycling methods will be designed. (V) Enhancement of the selectivity of ionic DESs and non-ionic DESs in several extraction techniques is needed to assist in the extracting and separating specific bioactive compounds from natural herbal medicine.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Data availability

No data was used for the research described in the article.

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