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Sustainable extraction of phytochemicals from agricultural and food by-products using eutectic solvents and their integration into functional materials

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Agricultural production plays a vital role in ensuring human nutrition, supplying approximately 80% of the food consumed globally. However, its intensive nature generates substantial amounts of by-products and waste, leading to significant environmental impacts, including soil, air, and water pollution. In this context, the repurposing and valorization of agricultural residues present both a challenge and an opportunity, particularly through the extraction of phytochemicals and nutraceuticals, which exhibit diverse and valuable biological activities. Over the past two decades, deep eutectic solvents (DESs) and their natural analogs (NaDESs) have emerged as promising, sustainable media for phytochemical extraction, offering simplicity, energy efficiency, and tunable properties. As a novel class of designer solvents, DESs are recognized for their green credentials and compositional flexibility, with their physicochemical characteristics determined mainly by the nature and ratio of their components. This review summarizes key methodologies for extracting phytochemicals and nutraceuticals from agricultural and agro-industrial by-products and waste, emphasizing the structure–property–function relationships of the DESs employed. It further evaluates the integration of DES-derived extracts into the development of bio-based materials for use in agriculture, food, and pharmaceutical applications. Special attention is given to the physicochemical parameters of DESs that govern their extraction performance and influence the transformation of bioactive compounds into sustainable functional materials, such as eutectogels. Finally, the review outlines future perspectives and critical steps toward optimizing the use of DESs for the valorization of agricultural residues and their conversion into high-value, functional products.

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Sustainability spotlight

Agricultural production sustains global nutrition but has long generated vast amounts of waste, leading to soil, water, and air pollution. Over the past two decades, efforts to address this challenge have increasingly focused on reducing environmental burdens while unlocking economic value from agricultural by-products. A major advancement has been the use of deep eutectic solvents (DESs) and their natural analogues (NaDESs), which offer energy-efficient, tunable, and environmentally friendly media for extracting phytochemicals and nutraceuticals. Importantly, DESs containing these bioactives can be directly transformed into functional bio-based materials with applications in agriculture, food, and pharmaceuticals, realizing their full potential. This progress aligns with the UN Sustainable Development Goals, particularly SDG 12, SDG 9, and SDG 3, advancing circular economies and sustainable resource use.

Introduction

Intensive agriculture underpins the global food supply, providing at least 80% of the food consumed worldwide—

a share expected to increase in the coming decades.¹ Major crops by annual production include sugarcane (1.86 billion tonnes), maize (1.21 billion tonnes), rice (787 million tonnes), wheat (771 million tonnes), and areca nut (416 million tonnes).² Such high productivity is accompanied by comparable volumes of waste and by-products, whose improper disposal—through open-air burning, dumping into water bodies, or uncontrolled leaching—can release toxic volatile organic compounds, promote pest proliferation, generate foul odors, and emit fine particulate matter.³ The food industry further contributes substantial waste streams from fruit, vegetable, grain, and seed

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processing, discarding shells, seeds, pulp, leaves, and whole fruits, thereby losing both nutritional and economic value. This wastage undermines food security and hinders progress toward circular economy and sustainability goals. Effective valorization of these diverse agricultural and food residues requires coordinated, multidisciplinary approaches to enable their sustainable transformation and upcycling.⁴

Over the past two decades, the quest for greener extraction strategies has turned its attention to deep eutectic solvents (DESs)—a versatile family of designer solvents that includes natural analogues (NaDES) and other low-transition-temperature mixtures. DESs are eutectic blends of Lewis or Brønsted acids and bases-hydrogen bond donors (HBDs) and acceptors (HBAs)—whose melting point is markedly lower than those of their individual components, yielding liquids at or near room temperature. By varying molecular species and molar ratios, DESs offer tunable physicochemical properties, enabling their application across fundamental research and technological innovation.^{5,6}

A defining strength of DESs in phytochemical extraction is their exceptional compositional plasticity, enabling solvent properties that span from hydrophilic (water-soluble) to non-volatile and hydrophobic. This tunability enables precise control over polarity, viscosity, acidity–basicity, and ionicity, facilitating the design of task-specific solvents when coupled with established extraction techniques, such as ultrasonication, microwaves, or enzyme-assisted methods. Many DESs can be synthesized from safe, readily available feedstocks commonly used in the agricultural, pharmaceutical, and food industries. Formulations can be tailored for low volatility, biodegradability, non-toxicity, recyclability, and other “green” credentials—attributes that are not inherent to all DESs but emerge from deliberate design. Their simple preparation, achieved through direct mixing, further supports the inherent scalability.^{7,8}

DESs are becoming a leading green technology for extracting phytochemicals from diverse agricultural wastes, competing with alternatives such as ionic liquids in terms of cost, infrastructure, and safety, generally. They offer a clear advantage over volatile organic compounds (VOCs)—including toxic chlorinated and fluorinated solvents—by virtually eliminating volatility, a key driver of air pollution and toxicity.⁹ Yet, this very attribute poses a challenge: in many downstream applications, such as food, cosmetics, pharmaceuticals, and dyes, DES-based extracts require resuspension or dissolution in conventional solvents for further processing. In some cases, recovery of phytochemicals from DESs has relied on VOCs and other reagents; the technology sought to replace.¹⁰ As a result, after significant optimization to selectively extract high-purity compounds from complex matrices, the reintroduction of VOCs, acids, or other harsh solvents undermines the environmental gains initially pursued, raising questions about the true extent of their sustainability.

We propose that a viable path forward lies in embedding DES-based phytochemical extraction within a circularity framework of green chemistry. In this approach, the DES functions not only as the extraction medium but also as the excipient for subsequent processing, eliminating the need for

secondary by-products, additional separations, or further extraction steps—critically, without resorting to VOCs or other solvents. This strategy could extend the shelf life of labile, photosensitive phytochemicals, as tailored DESs can mimic their native biochemical environments, thereby enhancing stability.¹¹ DESs can also serve as precursors for soft materials, such as eutectogels, waxes, creams, and microcapsules, with applications in agriculture,¹² food,¹³ and pharmaceuticals.⁷ Eutectogels—polymeric or colloidal systems entrapping DESs—, in particular, can be engineered into edible coatings, freshness indicators, controlled drug-delivery systems, and wearable sensors offering mechanical, thermal, and functional performance superior to many conventional materials.^{14,15} Harnessing phytochemicals from agricultural and food-industry by-products for such sustainable functional biomaterials presents a promising pathway toward circular, high-value applications.

This review surveys recent advances in the application of DESs for extracting phytochemicals—including polyphenols, phenolic acids, flavonoids, carotenoids, essential oils, saponins, and alkaloids—from agricultural waste and food-industry by-products. It examines the complexity of phytochemical-rich plant matrices, *i.e.*, recalcitrant and completely lignified biomasses, and the physicochemical attributes of DESs that dictate extraction and solubilization efficiency. The discussion covers DES classification, natural analogues, and the rational selection of HBDs and HBAs. Green-assisted extraction methods—such as enzyme-, ultrasound-, and microwave-assisted techniques—are assessed, with guidance on key operational parameters and the advantages of DES over conventional solvents. The review also addresses ternary systems incorporating water and hydrophobic DESs (HDES) for nonpolar targets, and emphasizes structure–property–function relationships. Strategies for isolating and purifying DES-derived extracts are outlined alongside approaches that retain the complete DES-phytochemical mixture to produce functional soft materials—such as eutectogels, edible films, emulsions, creams, waxes, sprays, pigments, and nutraceuticals—within a sustainability framework. As a case study, the Folin–Ciocalteu assay is provided along with troubleshooting guidance and alternative analytical options for quantifying total phenolic compounds (TPC) in botanical extracts.

Figures on wastes and by-products in agriculture and food industries

Agricultural wastes comprise non-edible plant parts—leaves, stems, roots, seeds—as well as damaged, malformed, or off-grade fruits arising during harvest, handling, and processing. Food industry by-products include both inedible fractions and edible components excluded from final products, such as pomace, fiber, bagasse, shells, peels, and seeds, generated in the production of juices, sauces, frozen or canned goods, and minimally processed foods.¹⁶

Global agricultural waste generation is estimated at 2.8 billion tons annually, representing nearly one-third of all food



produced. In the United States alone, projections indicate 320 million tons of agricultural residues by 2030, with corn stover accounting for 85% of this total.¹⁷ These wastes contribute substantially to greenhouse gas emissions and the accumulation of dry matter. In 2020, residues from crops such as corn, rice, wheat, and soybeans emitted 213.98 kilotons of N₂O in the Americas, 331.41 kilotons in Asia, and 117.39 kilotons in Europe.¹⁸ Burning these residues further yielded significant dry matter—201.98 million tons from corn, 90.31 million tons from rice, 87.60 million tons from wheat, and 17.20 million tons from sugarcane.¹⁹

The food industry similarly produces vast waste streams. Each year, more than 4.2 million tons of apple pomace, 2.88 million tons of olive pomace, and 1 20 000 tons of rice husks are generated worldwide. In Europe alone, cereal processing yields 45 000 tons of waste annually. According to the United Nations (UN),²⁰ 931 million tons of food—17% of global production—were wasted in 2019. Meanwhile, the Food and Agriculture Organization (FAO) data indicate that 13.3% of food is lost between production and consumption due to inefficiencies in harvesting, storage, transport, and marketing. In the United States, the largest share of food losses occurs at the consumer level (Fig. 1).^{1,21}

These vast waste streams constitute a valuable reservoir of phytochemicals and lignocellulosic feedstocks, which could be efficiently valorized using DESs. Unlocking this potential requires overcoming key challenges: (1) selective extraction of target phytochemicals, (2) robust green metrics for DESs, (3) rational solvent design, (4) biocompatibility, (5) scalability, and (6) harnessing synergistic effects between DES properties and extracted compounds.

What are DESs?

DESs were first reported by Abbott *et al.*,²² who observed a pronounced melting-point depression in a 1 : 2 molar mixture of choline chloride (ChCl) (melting point of 302 °C) and urea (melting point of 133 °C), yielding a eutectic point at 12 °C. This low freezing temperature rendered the anhydrous mixture liquid at room temperature, allowing it to be used as a solvent. Their work demonstrated that quaternary ammonium salts combined with amides can form low-melting eutectic systems with promising solvent properties—a concept later expanded to include HBDs such as carboxylic acids, amides, and alcohols.²³ The melting-point depression observed in DESs arises from hydrogen bonding and other noncovalent interactions between the HBD and HBA. Thermodynamically, they can be described as mixtures exhibiting enthalpy-driven negative deviations from ideality, forming a liquid at the target temperature—a behavior confirmed by phase diagrams.²⁴ In practical terms, a DES remains liquid under operating conditions even when one or more of its pure components would otherwise be solid and unsuitable as a solvent.

Beyond their low melting points, several attributes underpin the suitability of DESs as solvents. They can be readily prepared by mixing and gently stirring the HBA and HBD at mild temperatures (≈ 40 – 80 °C), achieving 100% atom economy, as their formation is driven primarily by hydrogen bonding rather than covalent bond-forming reactions, thus generating no waste.²⁵ DESs are generally non-flammable, exhibit low toxicity and volatility, and display chemical and thermal stability—although the nature of their constituents inherently determines these properties. Due to the vast array of compounds that can

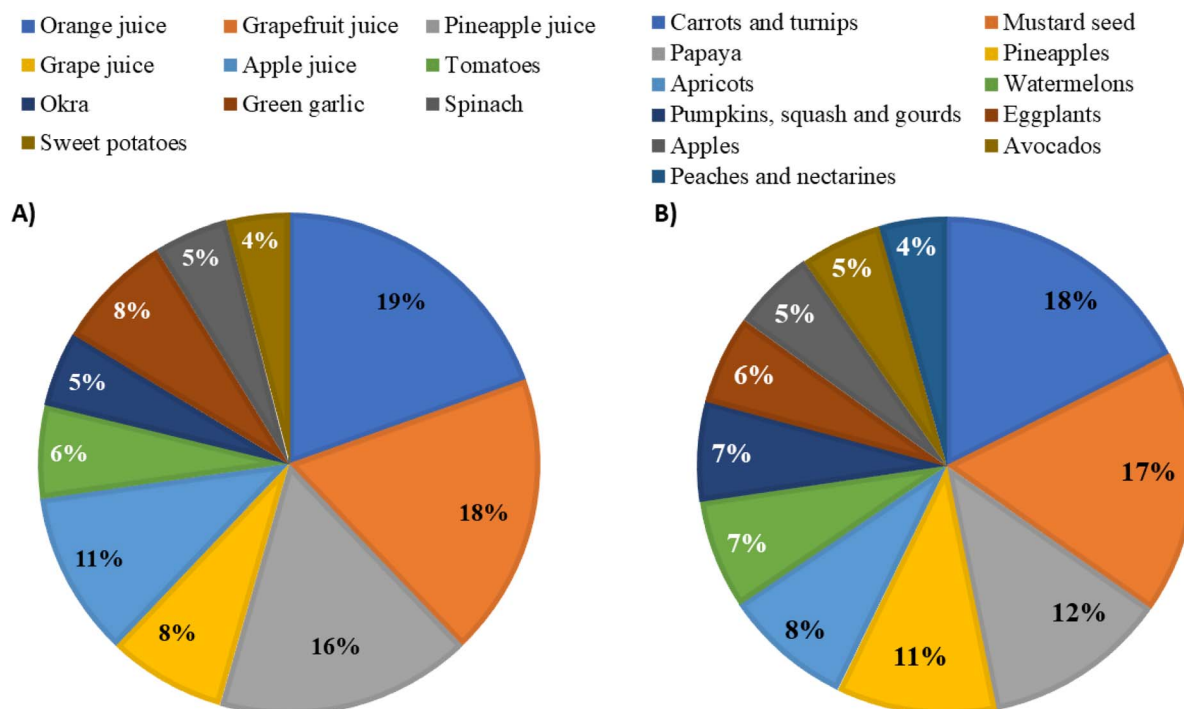


Fig. 1 (A) Food losses occur in the entire production and marketing chain. (B) Food losses in retail. The pie charts were elaborated using data from the FAO Food Loss and Waste Database.²¹



Table 1 Classification of DESs

Type	Combination
I	Quaternary ammonium salt + anhydrous metal halide
II	Quaternary ammonium salt + hydrated metal halide
III	Quaternary ammonium salt + HBD (amides, carboxylic acids, and alcohols)
IV	Metal chloride hydrate + HBD (amide, alcohol, acids, <i>etc.</i>)
V	Non-ionic HBA + non-ionic HBD

serve as HBAs and HBDs, DESs offer exceptional tunability, allowing for the adjustment of polarity, viscosity, conductivity, and other critical physicochemical properties according to the intended application.²⁶ Based on the chemical structures of the HBA–HBD pairs, DESs have been classified into five principal types, as summarized in Table 1.

DESs are classified into five main types. Type I combines quaternary ammonium salts with anhydrous metal halides, although their high melting points limit the range of suitable halides. Type II pairs quaternary ammonium salts with hydrated metal halides, which are more cost-effective for industrial use. Type III—the most common and versatile—mixes quaternary ammonium salts (*e.g.*, ChCl) with organic HBDs such as amides, carboxylic acids, or alcohols, yielding biodegradable, low-cost, and low-toxicity solvents whose properties depend on composition. Type IV merges type II and III features by combining a metal halide with an HBD, whereas type V employs non-ionic HBAs and HBDs, often resulting in hydrophobic DESs.^{27,28}

Challenges in extracting phytochemicals from agro-food wastes and opportunities offered by DESs

Agricultural wastes contribute an estimated 1.5×10^{11} tonnes annually to global lignocellulosic biomass. These residues, primarily stalks and roots, contain 80–85% lignocellulosic material—mainly cellulose, hemicellulose, and lignin. For instance, rice, wheat, and corn biomass typically comprises 32–47% cellulose, 19–30% hemicellulose, and 5–24% lignin.^{29,30}

Conventional solvents, such as hexane, chloroform, and methylene chloride, are widely used for phytochemical extraction; however, they are highly volatile and toxic to both the environment and human health.³¹ Their efficiency is further limited because many phytochemicals—particularly phenolics—are bound to structural polymers in biomass, especially seeds and stalks. Consequently, harsh pretreatments involving acid or alkali media, enzymatic, mechanical, fermentative, or thermal methods are often required, which increases time, cost, and environmental impact, and potentially leaves solvent residues that hinder the direct use of the extracts.

Agricultural lignocellulosic wastes are rich in polyphenols and phenolic acids—principally hydroxybenzoic and hydroxycinnamic acids—often classified as bound phenolics. Other secondary metabolites, including flavonoids, saponins,

terpenes, and alkaloids, are also present. Phenolic acids are typically linked to cellulose and lignin through ionic or covalent bonds, or trapped within primary cell walls.³² The effective release of these compounds requires the disruption of these resilient interactions and enhanced solubilization (Fig. 2). DESs have proven effective in delignifying and depolymerizing robust plant tissues, as highlighted in recent reviews.^{33–35}

DESs are also widely employed to extract flavonoids and other phytochemicals from agricultural wastes and food by-products. Key parameters influencing their performance include the nature of the HBD and HBA, their molar ratio, and water content, which together modulate properties such as acidity, polarity, and viscosity. For example, DESs formulated with organic acids as HBDs have been successfully employed to delignify garlic skins and green onion roots; in these systems, the increased hydrogen-bond acidity promotes the cleavage of lignin ether linkages (*e.g.*, β -O-4) and phenolic interactions, disrupting the lignocellulosic network and thereby enhancing the accessibility of cellulose and hemicellulose to subsequent hydrolysis.³⁶ In this context, a dual-purpose approach can be envisioned in which DESs are rationally designed to both delignify agricultural residues and, in parallel, solubilize and recover significant quantities of bound phytochemicals. This represents a major advantage compared to conventional organic solvents, which are unable to delignify biomass on their own and therefore extract only the fraction of freely available phenolic compounds.

The generally low toxicity of DESs makes them suitable for phytochemical extraction, allowing for the direct application of extracts in the food, pharmaceutical, and biomedical sectors. They can be formulated from safe, natural compounds already approved for food use, are readily biodegradable, and have a low environmental footprint. Their reusability enhances cost-effectiveness and scalability, while tunable hydrophilicity or hydrophobicity broadens their scope of application.³⁷ DES-derived extracts exhibit negligible vapor pressure and extended stability and can be obtained as ready-to-use products.³⁸ Moreover, their economic viability has been assessed to ensure alignment with environmental, industrial, and social sustainability in by-product valorization. However, following the perspective of Schaeffer and Coutinho³⁹ the capacity of DESs to overcome solubility challenges of target compounds—particularly those originating from biomass and other resilient matrices through liquefaction—should take precedence over the often-invoked yet experimentally unsubstantiated claims regarding their green, nontoxic, and biodegradable nature.



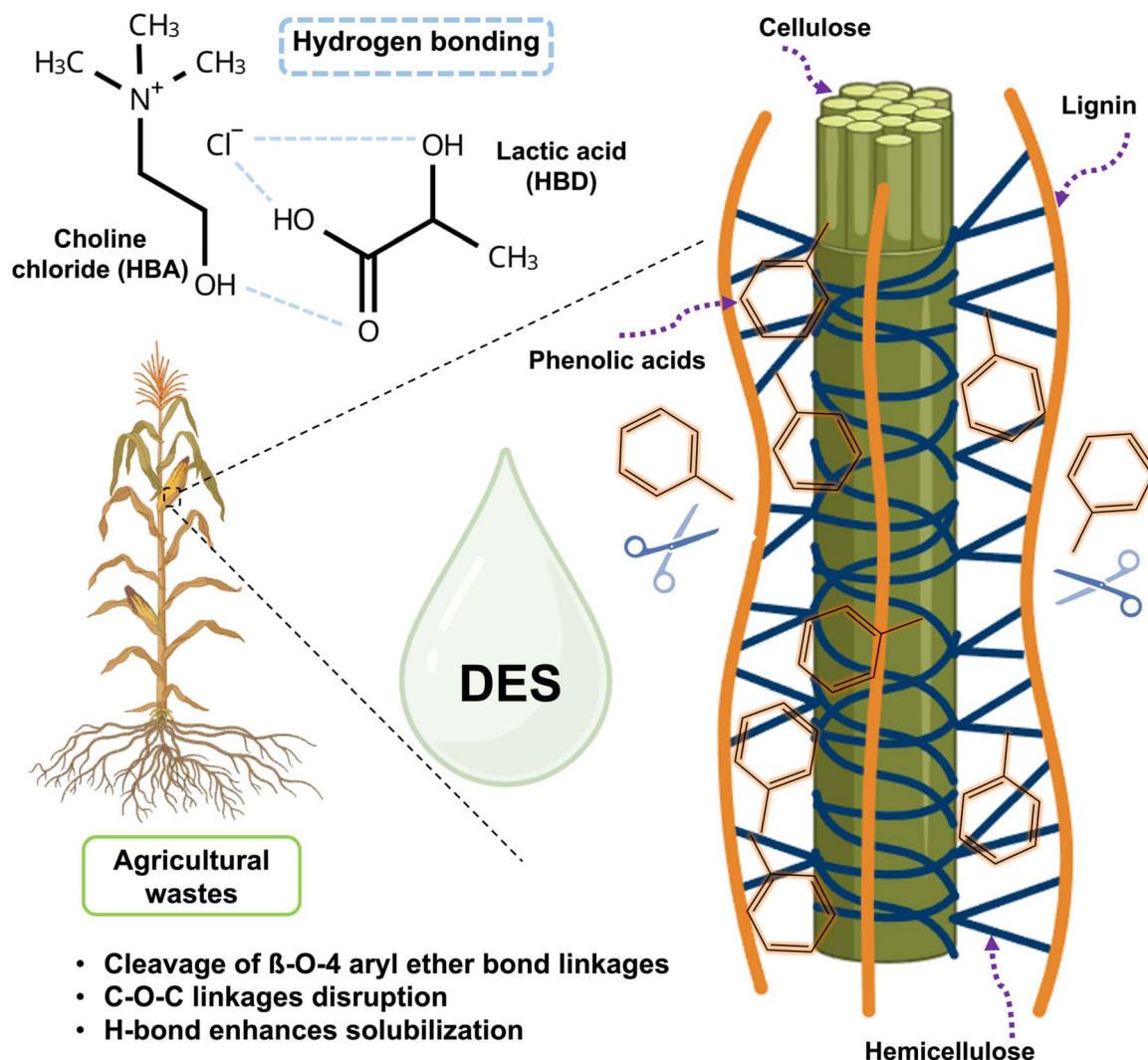


Fig. 2 Bound phenolic extraction by DESs. The DESs must break the covalent bonds (ether, ester, and carbon-carbon) between hydroxyl and carboxyl groups in phenolic compounds, lignin, and structural polymers and proteins in the cell wall. Figure created with BioRender®.

Overview of DES-coupled extraction techniques for phytochemical recovery from agro-food wastes

Current efforts in extraction technology focus on reducing the use of conventional solvents, driving the adoption of eco-friendly, high-efficiency alternatives.⁴⁰ Traditional hydrophilic and lipophilic solvents, long used for phytochemical recovery, present high toxicity, poor green metrics, and significant limitations for valorizing agricultural and food-industry by-products—particularly when intended for human, plant, or animal health applications. These methods are time- and solvent-intensive, have low selectivity, can degrade thermolabile compounds due to elevated temperatures, and generate substantial waste. They also require costly downstream operations, and residual solvents often remain in the extracts due to incomplete removal.^{41,42}

Emerging extraction techniques surpass conventional methods by reducing waste, maximizing the use of raw material, shortening processing times, operating at ambient

conditions, improving yields, and enhancing selectivity for target compounds. Many align with green chemistry principles, emphasizing sustainable inputs, lower environmental impact, and cost-effectiveness.³¹ These approaches often utilize affordable, alternative solvents and avoid the use of complex or costly equipment. Table 2 presents a summary of the main properties and parameters of emerging and conventional extraction methodologies.

DESs can be coupled with assisted techniques—such as ultrasound, microwave, and enzyme-assisted extraction—to further increase yields compared with conventional methods. The general mechanism of assisted methods is their ability to break down the phytochemical storage in plant tissues, such as vacuoles, cell walls (bound forms), epidermal tissues, plastids, and seed tissues, thereby facilitating the interaction and solubilization of the compound with DES.^{31,43} On the other hand, the extraction mechanism, by which DESs are able to extract higher amounts of phytochemicals, is primarily driven by inter- and supramolecular interactions—particularly hydrogen



Table 2 Overview of phytochemical emerging and conventional extraction methodologies^{43–47}

Type	Method	Temperature	Time	Type of solvent	Solvent consumed	Phytochemical polarity	Key parameters
Conventional	Maceration, percolation, decoction, reflux, Soxhlet	Room temperature – 120 °C	Longer (hours–days)	Aqueous, organic	Large	Non-polar and polar compounds	Temperature, contact time, pH, particle size, solid–liquid ratio, and stirring
Emerging	Pressurized liquid	50–200 °C	Short time (minutes)	Aqueous, traditional, or emerging solvents	Small	Non-polar and polar compounds	Time, temperature, pressure, solid–liquid ratio, particle size
	Supercritical fluids	35–50 °C	Short–moderate (minutes–hours)	CO ₂ and co-solvents, <i>i.e.</i> , ethanol	Small	Non-polar and polar compounds	Pressure, time, co-solvent ratio, temperature
	Ultrasound	Room temperature – 80 °C	Short (minutes)	Aqueous, traditional, or emerging solvents	Small	Non-polar and polar compounds	Amplitude, frequency, time, temperature, and cycle solid–liquid ratio
	Microwave	Room temperature – 100 °C	Short (minutes)	Aqueous, traditional, or emerging solvents	Small	Non-polar and polar compounds	Cycle, temperature, time, power, stirring, solid–liquid ratio
	Pulsed electric field	Room temperature – 80 °C	Short (minutes)	Aqueous, traditional, or emerging solvents	Small	Non-polar and polar compounds	Voltage, temperature, work cycle, electric field, pulse frequency
	Enzymatic	Room temperature	Moderate (hours–days)	Aqueous and emerging solvents	Moderate	Non-polar and polar compounds	Enzyme, temperature, time, pH, substrate, and solid–liquid ratio

bonding and π – π stacking—between DES components and secondary metabolites. For instance, the hydroxyl-rich structure of flavonoids favors the formation of extensive hydrogen-bond networks with DES constituents, enhancing solubility and recovery (Fig. 3).^{8,11,48} Studies have shown that in specific cases, higher ChCl molar ratios strengthen ionic interactions with plant cell walls, promoting their disruption and the release of flavonoids.⁴⁹ The following section provides a concise overview of the key characteristics and extraction mechanisms of the assisted methods most frequently employed in combination with DESs.

Ultrasound-assisted extraction

Ultrasound-assisted extraction is among the most efficient techniques due to its low energy demand, minimal waste generation, and ability to markedly enhance extraction yield.⁵⁰ Its underlying mechanism relies on acoustic cavitation generated by ultrasonic waves; the formation and collapse of microbubbles produce localized microjets that disrupt plant cell walls, create microcavities, and facilitate DES penetration, thereby improving phytochemical solubilization and mass transfer.⁴³ When using probe or bath ultrasonicators, operating parameters such as frequency and amplitude are critical, as they directly influence cavitation intensity and should be

optimized using response surface methodologies. However, excessive ultrasonic power may induce the formation of free radicals and undesirable structural changes in sensitive phytochemicals. For this reason, moderate intensities, short treatment times, and, when possible, pulsed operation are recommended.⁴⁰ One of the key advantages of DES over low-viscosity volatile solvents, such as ethanol, methanol, acetone, or hexane, is its moderate viscosity and non-volatile nature, which enables its use in probe-based ultrasonic systems where conventional solvents rapidly evaporate upon temperature rise, thereby compromising extraction performance. Furthermore, their higher viscosity can provide a protective medium for phytochemicals against the intense acoustic energy generated by ultrasonic equipment, thereby mitigating degradation. Recent excellent reviews highlight ultrasound-assisted DES extraction as one of the most widely adopted techniques due to its consistently high extraction yields.^{51,52}

Microwave-assisted extraction

Microwave-assisted extraction relies on the application of electromagnetic radiation within the 0.3–300 GHz frequency range. In this technique, microwaves directly irradiate the sample, inducing rapid internal heating through dipolar rotation and ionic conduction. The resulting temperature rise causes the



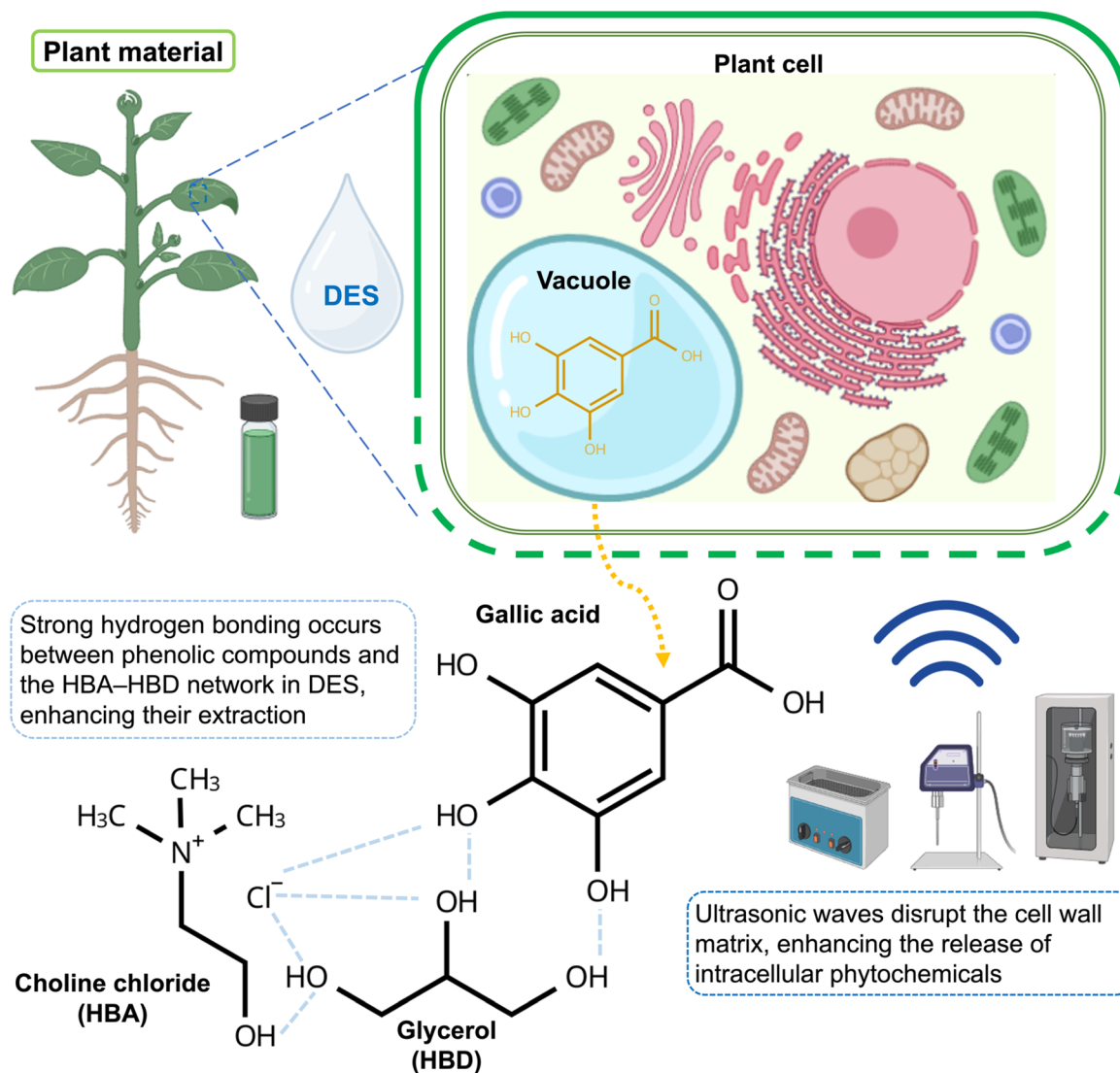


Fig. 3 The general mechanism by which DESs manage to solubilize and extract flavonoids from natural sources. Figures created with BioRender®.

disruption of plant cell walls, promoting the release of phytochemicals into the DES.⁵³ Two key transport phenomena govern the process: thermally driven diffusion resulting from temperature gradients, and enhanced mass transfer across disrupted cellular barriers. Owing to their short extraction times and reduced energy requirements, microwave-based approaches are considered environmentally sustainable. Nevertheless, the use of high microwave power (*e.g.*, 900 W) may degrade thermolabile compounds, consequently impairing extraction efficiency. Therefore, moderate power levels and carefully controlled exposure are recommended.⁵⁴ Microwave-assisted extraction using DES has been extensively explored and has demonstrated excellent extraction yields (>86%)⁵⁵ attributed to the intrinsic properties of these solvents, including their viscosity, density, and low vapor pressure, which prevents evaporation even under microwave irradiation. This combination enables efficient energy utilization, short processing times, and highly favorable extraction outcomes.⁵⁵

Enzyme-assisted extraction

Enzymatic-assisted extraction represents an efficient and environmentally sustainable strategy for phytochemical recovery, as it enables the targeted degradation of plant cell wall polymers—such as cellulose, hemicellulose, lignin, and pectin—thereby facilitating the release of bound secondary metabolites. Unlike conventional solvent-based approaches, it employs GRAS-certified enzymes that operate under mild conditions (typically <40 °C), reducing energy consumption and minimizing environmental burdens, as confirmed by life cycle analyses.⁴¹ Due to their high specificity, enzymes such as pectinases, cellulases, and hemicellulases hydrolyze structural polysaccharides at specific active sites, thereby accelerating tissue disruption and enhancing extraction yields. Optimal performance depends on the selection of an appropriate enzyme, pH, substrate characteristics, temperature, extraction time, and solid-to-liquid ratio.⁵⁶ The use of enzyme cocktails (*e.g.*, cellulases, papain, amylases, lipases, pectinases, and





Table 3 Phytochemicals extracted from agro-food wastes using DES coupled with assisted methods^a

Plant material	Phytochemical	DES	Assisted method	DES extraction efficiency	Traditional solvent extraction efficiency	Ref.
<i>Beta vulgaris</i> waste (stalks)	TPC	ChCl : urea 1 : 2 mol ratio	Microwave	0.5 mg GAE g ⁻¹ FW	Water 0.14 mg GAE g ⁻¹ FW	60
Jackfruit peel waste	TPC	ChCl : lactic acid 1 : 2 molar ratio with 23% wt. water	Ultrasound and microwave	53.16 ± 1.23 mg GAE g ⁻¹ DW	Hydroethanolic ~20 mg GAE g ⁻¹ DW	61
Strawberry waste	Hesperidin, isoquercetin, catechin, quercetin, luteolin, gallic acid	ChCl : lactic acid 1 : 5 molar with 30% of water	Ultrasound and stirring	Hesperidin: 1433 µg g ⁻¹ Isoquercetin: 2348 µg g ⁻¹ Catechin: 621 µg g ⁻¹ Quercetin: 593 µg g ⁻¹ Luteolin: 169 µg g ⁻¹ Gallic acid: 49.4 µg g ⁻¹ 2.980 mg g ⁻¹ DW	Ethanolic hesperidin: 961 µg g ⁻¹ Isoquercetin: 1850 µg g ⁻¹ Catechin: 474 µg g ⁻¹ Quercetin: 85.3 µg g ⁻¹ Luteolin: 79.8 µg g ⁻¹ Gallic acid: 41.5 µg g ⁻¹ EtOH ~1.5 mg g ⁻¹ DW	62
Peanut leaves and stem wastes	TFC	ChCl : acetic acid 1 : 2 mol ratio with 27% of water	Ultrasound			63
Citrus peel waste	Polymethoxylated and glycosylated flavonoids	ChCl : levulinic acid : <i>N</i> -methyl urea 1 : 1.2 : 0.8 mol ratio with 80% water v/v	Ultrasound	A sum of flavonoids: 65.82 mg g ⁻¹	MeOH a sum of flavonoids: 53.08 mg g ⁻¹	64
Onion peel	Tannic acid	ChCl : urea 1 : 1 mol ratio with 75 mL of water	Ultrasound	641.16 ± 0.01 µg g ⁻¹	MeOH 368.99 ± 0.02 µg g ⁻¹	65
Red grape pomace	TPC	Betaine : urea 1 : 2 mol ratio with 40 wt% water	Solid-liquid extraction	12% wt DW	Water 5.5% wt DW EtOH 6% wt DW	66
Orange peel waste	D-limonene	ChCl : glycerol 1 : 2 mol ratio with 30% water	Homogenized	3.7 mg g ⁻¹ FW	<i>n</i> -hexane 6.4 mg g ⁻¹ FW	67
<i>Scutellaria baicalensis</i> stem bark	Baicalin, scutellarein, wogonin, wogonoside, oroxylin A, oroxyloside	Citric acid : β-alanine 1 : 1 mol ratio with 50% w/w water	Maceration and ultrasound	A sum of flavonoids: 151.2 ± 8.4 µg mg ⁻¹ DW	EtOH 70% a sum of flavonoids: 68.2 ± 19.8 µg mg ⁻¹ DW	68
Tartary buckwheat hull	Rutin	ChCl : glycerol 1 : 1 mol ratio with 20% w/w water	Ultrasound	9.6 mg g ⁻¹ DW	MeOH 80% <4 mg g ⁻¹ DW	69
Blueberry-peel	Total anthocyanins	ChCl : lactic acid 1 : 1 mol ratio with 25% v/v water	Microwave	25.83 mg g ⁻¹ DW	Acidified hydroalcoholic solution 22.70 mg g ⁻¹ DW	70
<i>Carya cathayensis</i> Sarg. peels	TFC	ChCl : malic acid 1.5 : 1 mol ratio	Pulse-ultrasound	793.17 ± 5.33 mg QE g ⁻¹ DW	MeOH 80% 400.04 ± 3.07 QE g ⁻¹ DW	71
Sunflower wastes	Lutein, zeaxanthin, antheraxanthin, violaxanthin	D, L-menthol : D, L-lactic acid 1 : 2 mol ratio	0.58% of the multi-enzyme complex viscozyme	Total carotenoids: 1449 mg per 100 g	Total carotenoids: hexane 20 mg per 100 g	72
Olive leaves	Hydroxytyrosol	Citric acid : glycine: water 2 : 1:1 mol ratio	Cellic CTec2, 200 mg mL ⁻¹ , reaction time 120 min	87 ppm	Water ≈ 40 ppm	73
Jujube fruits	TFC	ChCl : urea 1 : 3 mol ratio	Cellulose/pectinase ratio 2 : 1 w/w, pH 5.10. Extraction time 180 min	6.85 mg RE g ⁻¹	3.61 mg RE g ⁻¹	74

^a TPC (total phenolic content). TFC (total flavonoid content). FW (fresh weight). GAE (gallic acid equivalent). DW (dry weight). QE (quercetin equivalent). RE (rutin equivalent).

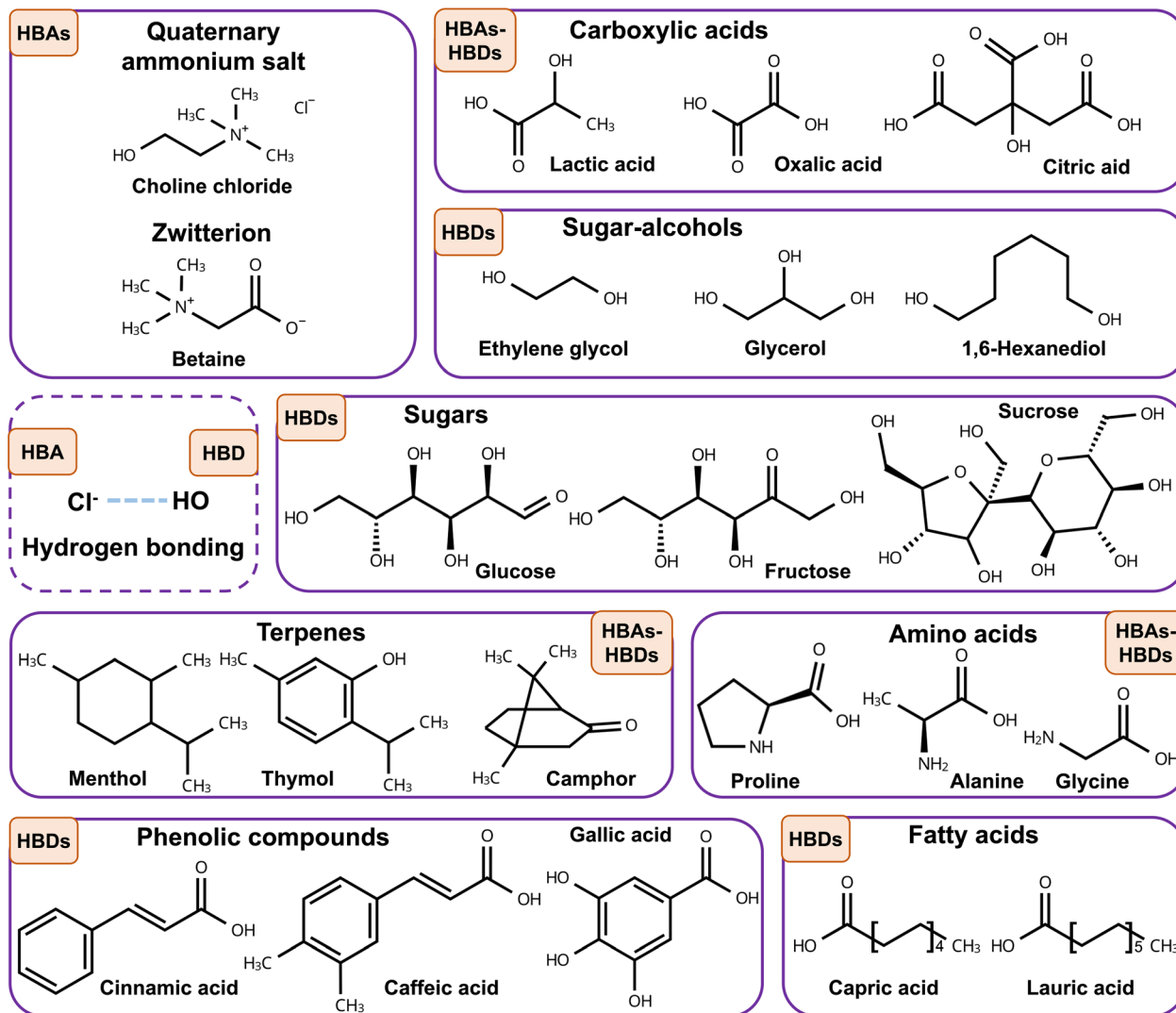


Fig. 4 Representative HBAs and HBDs. Note that carboxylic acids, terpenes, and amino acids can function as both HBAs and HBDs. Chemical structures were drawn using MolDraw.

hemicellulases) can further enhance delignification and significantly shorten process times through synergistic action, which is particularly advantageous for extracting phytochemicals from recalcitrant matrices.⁵⁷ Conversely, enzyme-assisted DES systems leverage their strong hydrogen-bond networks, tunable polarity, and non-volatile nature to preserve enzyme conformation while enhancing substrate solvation and catalytic accessibility. This approach reveals substantial biotechnological potential, which has been increasingly explored in recent years, often outperforming conventional solvent-based extraction. Beyond acting as pretreatment media for plant biomass, DES can also function as catalytic environments that host immobilized or freely dissolved enzymes, improving their stability and activity and thus enhancing overall extraction efficiency.^{58,59}

In Table 3, selected examples of DES-assisted extraction coupling ultrasonic, microwave, and enzymatic extractions are presented, highlighting that in most cases, extraction with DES outperformed traditional solvents.

HBD and HBA and their molar ratio choice determine the extraction properties (designer solvents)

Given the principles governing the formation of DESs, a vast range of possible HBA–HBD binary combinations exists (Fig. 4). The compositional flexibility of DESs—either by changing one component or adjusting their molar ratio—allows the design of solvents with specific physicochemical properties, such as viscosity, polarity, density, and acidity. These tunable properties directly influence the efficiency and yield of phytochemical extraction.⁷⁵ These properties are determined by the nature of the starting components and their intermolecular interactions. While extractions are not typically conducted at the eutectic point, the DES must remain above the liquidus curve in the solid–liquid phase diagram.²⁴

Among the most widely used eutectic systems for phytochemical extraction are DESs, NaDESs, and HDESs, particularly those formed with quaternary ammonium salts such as ChCl and betaine as HBAs, followed by amino acids like glycine and L-



proline. Common HBDs include polyols (*e.g.*, glycerol), carboxylic acids (*e.g.*, lactic and citric acids), and sugars (*e.g.*, glucose and fructose), most of which are GRAS-certified and widely used in food and pharmaceutical applications.⁷⁶ In HDEs, HBAs typically comprise monoterpenes such as thymol, menthol, borneol, and camphor, whereas HBDs often include fatty acids—such as myristic, octanoic, decanoic, dodecanoic, lauric, and pyruvic acids—along with other fatty and carboxylic acids.⁷⁷

The vast array of possible HBA–HBD combinations offers significant scope for designing DESs with tailored physicochemical properties. These properties depend not only on the intrinsic characteristics of the components but also on their intermolecular interactions, a feature that underpins the use of DESs as “designer solvents” for the extraction and stabilization of natural products.^{11,78}

In general, several studies indicate that the most used HBAs for the extraction of phenolic compounds are ChCl, followed by betaine to a lesser extent. Regarding HBDs, polyols such as glycerol, ethylene glycol, and butanediol are among the most commonly employed, followed by organic acids including lactic, citric, malic, and levulinic acids, and, finally, sugars such as sucrose or glucose.^{51,76} Nevertheless, the optimal selection of DES must consider the characteristics of the plant matrix, the physicochemical properties of the target metabolites, and the intended application of the final extract.

In a recent review, Jiménez-Ortega *et al.*⁸ discuss the use of bioactive-antioxidant HBAs and HBDs to create a cooperative and synergistic effect with extracted phytochemicals. In this context, certain phenolic acids, flavonoids, or other secondary metabolites can act as HBDs due to their multiple hydroxyl groups, generating a bioactive DES, for multiple food and pharmacological purposes.

Regarding the molar ratio between HBD and HBA effect on phytochemical extraction, analysis of the 60 studies included exclusively in the tables of the present review (flavonoids = 48; terpenes = 10; alkaloids = 6; saponins = 6) reveals a clear dependence on the target metabolite. For phenolic compounds, including flavonoids, 33% of the reviewed studies employed a 1 : 1 HBA–HBD ratio, followed by 25% using 1 : 2 and 8% using 1 : 3, while HBA-enriched systems were less frequent (6% with 5 : 1 and 6% with 2 : 1). In terpene extraction, the 1 : 2 ratio was predominant (40%), followed by 1 : 1 (20%) and 1 : 3 (10%), with a smaller proportion of studies exploring HBA-rich formulations such as 2 : 1 and 3 : 1 (10% each). For alkaloids, half of the studies applied a 1 : 2 ratio, whereas saponin extraction was evenly distributed between 1 : 1 and 2 : 1 (33% each). In specific cases, such as extracting carotenoids from marigold flowers, higher yields were achieved (971.31 $\mu\text{g mg}^{-1}$ DW) with a 3 : 1 ChCl:glucose ratio. The strong hydrogen-bond network and optimal polarity of the DES facilitated tissue disruption and enhanced carotenoid diffusion.⁷⁹ Similarly, polyphenol extraction from broccoli stem waste showed superior performance at a 1 : 3 ChCl : urea ratio, as increasing the urea content tuned the solvent polarity and improved phenolic extraction.⁸⁰

Physicochemical properties of DES – viscosity, density, polarity, acidity, and surface tension define the phytochemical extraction capacity

A thorough analysis of the physicochemical properties of DESs—including viscosity, density, polarity, thermal stability, water content, molar ratio, and acidity—is critical for optimizing phytochemical extraction. Accordingly, the following sections offer an in-depth overview of the most relevant thermophysical and physicochemical parameters in this context.

Viscosity

Viscosity is a critical parameter in extraction processes, as DESs generally exhibit higher values (10–10 000 mPa s at room temperature) than conventional organic solvents, which can hinder mass transfer and handling. This relatively high viscosity stems from extensive hydrogen bonding between components, which restricts molecular mobility. While low-viscosity media, such as water (0.89 mPa s at room temperature), are preferable, viscosity issues in DESs can be mitigated by adding water—typically below 35 wt% in ChCl-based systems—or by increasing the extraction temperature.⁸¹ For example, in ChCl : urea (1 : 2), viscosity decreases from 1100 cP at 20 °C to 100 cP at 50 °C.²²

The nature of the HBD has a strong influence on DES viscosity. Polyol-based DESs generally exhibit lower viscosities than those with carboxylic acids or sugars, ranging from 20–7600 cP at 40 °C⁸² and 809–2279 mPa s at 25 °C, respectively.⁸³ Within polyols, longer-chain or isomeric glycols—such as 1,4-butanediol (112.18 mPa s at 20 °C)—exhibit higher viscosities than conventional glycols, including ethylene glycol (60 mPa s), 1,2-propanediol (94.5 mPa s), or 1,3-propanediol (69.74 mPa s). Additionally, viscosity tends to decrease as the polyol-to-HBA ratio increases.⁸⁴

Carboxylic acid-based DESs exhibit viscosities that depend on their functional group composition, the molar ratio of their constituents, and the physical state of the acid component. Solid acids, such as malic or citric acid with ChCl, yield higher viscosities (6000–7600 cP), whereas liquid acids, such as lactic or acetic acid, produce much lower values (10–1310 cP).⁸² For example, ChCl : lactic acid (20–1310 cP) and ChCl : acetic acid (10–400 cP) outperform high-viscosity systems, such as ChCl : citric acid (2390–6800 cP) in extracting phenolics from *Phoenix dactylifera* seeds.⁸²

Solid acids, such as malic or citric acid, with ChCl yield higher viscosities (6000–7600 cP), which increase with the acid content. In contrast, liquid acids like lactic or acetic acid result in much lower viscosities (10–1310 cP).⁸²

Liquid-state DESs with monocarboxylic acids, such as ChCl : lactic acid (20–1310 cP) and ChCl : acetic acid (10–400 cP), have shown superior performance in extracting phenolic compounds from *Phoenix dactylifera* seeds compared with higher-viscosity systems like ChCl : citric acid (2390–6800 cP) and ChCl : malic acid (1710–7600 cP).⁸² In practice, DES extractions are often



performed at temperatures above 40 °C which reduces viscosity *via* increased molar volume and molecular mobility, thereby enhancing the contact with biomass, resulting in an enhancement in mass transfer.

Emerging AI and machine learning models can now predict viscosities for large DES libraries based on HBA–HBD type, molar ratio, water content, and temperature, accelerating system design and solubility prediction for targeted phytochemical extraction. For example, data-driven models have been developed to predict the viscosity of more than 100 DESs, elucidating—through machine learning algorithms such as support vector regression (SVR), random forest (RF), neural networks (NN), and extreme gradient boosting (XGBoost)—that the physicochemical properties of the HBD play a predominant role in the viscosity of the system, together with its functional groups and the molar ratio relative to the HBA. Notably, higher HBD-to-HBA ratios were associated with a marked decrease in viscosity.⁸⁵

Density

The practical use of DESs in phytochemical extraction largely depends on their thermophysical properties, particularly density. Density—typically 0.8–1.8 g cm^{−3} for hydrophilic and hydrophobic DESs at 5–100 °C⁸⁶—is determined by the mass, size, and packing of HBA and HBD molecules, with more efficient packing yielding higher values. According to the Hole Theory, hydrogen-bond networks reduce free volume (“holes”), thereby increasing density.⁸⁷

Increased density enhances solvent penetration and its contact with plant tissues, improving solubilization and mass transfer. For example, DESs based on *n*-propanol (1.16 g cm^{−3}), 1,3-propanediol (1.38 g cm^{−3}), and 1,2,3-propanetriol (1.48 g cm^{−3}) show progressively higher densities with more hydroxyl groups, correlating with increased total phenolic (0.29 mg GAE) and flavonoid content (15.20 mg QE) in star anise extracts.⁸⁸ HBD type and molar ratio significantly influence density: polyol-based DESs (~1.04 g cm^{−3}) are generally less dense than those with carboxylic acids (~1.20 g cm^{−3}). In ChCl:polyol DESs, density increases slightly with molar ratio (*e.g.*, 1,4-butanediol: 1.04 to 1.06 g cm^{−3} from 1:2 to 1:4), while in ChCl:carboxylic acid systems, the increase is more pronounced (*e.g.*, oxalic acid: 1.20 to 1.23 g cm^{−3} from 1:1 to 1:2). Similar trends occur with urea-based DESs (1.16 to 1.19 g cm^{−3} from 1:1 to 1:3).⁸⁹

Polarity

Solvent polarity is a key factor in phytochemical extraction, as it governs solubility according to the “like dissolves like” principle. DESs offer tunable polarity, ranging from hydrophilic to hydrophobic, enabling the extraction of a diverse range of secondary metabolites, including hydrophobic and hydrophilic ones. Type III DESs based on ChCl or betaine are typically polar, with polarity modulated by the HBD; carboxylic acids confer the highest polarity, followed by sugars, amino acids, and polyols.⁸¹ Hydrated DESs often match water's polarity (~48 kcal mol^{−1}, normalized Reichardt polarity parameter—ENR—), as shown in xylitol:ChCl:water 1:2:3 molar ratio (48.21 kcal mol^{−1}) and glycerol:ChCl:water 2:1:1 molar ratio (49.55 kcal mol^{−1})

mixtures. Carboxylic acid-based DESs (*e.g.*, malic, tartaric, lactic, citric acids) display similar hydrophilicity (~47 kcal mol^{−1}).⁹⁰ In contrast, hydrophobic DESs (type V) employ HBAs and HBDs such as menthol, thymol, camphor, and fatty acids, targeting non-polar compounds like carotenoids. These exhibit ENR values of ~49–53.5 kcal mol^{−1}, *e.g.*, 1-menthol:camphor 1:1 molar ratio (53.26 kcal mol^{−1}) and lauric acid:octanoic acid 1:3 molar ratio (52.36 kcal mol^{−1}).⁹¹

In general, phenolic compounds are efficiently extracted using polyol- and carboxylic acid-based DESs and NaDES, which exhibit moderate-to-high polarity compared with conventional ethanol–water mixtures.⁹² Aglycone and glycosylated flavonoids display distinct extraction behaviors: anhydrous DES preferentially solubilize aglycones, whereas hydrated DES facilitate the extraction of glycosides, as the increased polarity induced by water enhances the solubility of the sugar moiety.¹¹ Conversely, non-polar secondary metabolites such as terpenes are more readily solubilized in hydrophobic DES, particularly those formulated with menthol, thymol, or fatty acids.⁸ Polarity strongly influences extraction selectivity. For example, ChCl:xylitol (2:1 molar ratio) and ChCl:1,2-propanediol (1:1 molar ratio) achieved high recovery of phenolics from virgin olive oil due to favorable polarity and hydrogen bonding.⁹³ Similarly, less polar DESs, such as ChCl:levulinic acid:*N*-methyl urea (1:1.2:0.8), yielded optimal amounts of polymethoxylated citrus flavonoids.⁶⁴

Finally, useful approaches have been proposed to correlate the Kamlet–Taft parameters (polarity descriptors) of DESs with their ability to dissolve lignocellulosic components, such as cellulose and lignin, thereby enabling the development of databases for the rational design of DES formulations for depolymerization or extraction of bound phenolics. Interestingly, DESs with β (Lewis basicity) values greater than 0.8 and a balanced β–α (0.35–0.90), such as acidic ones, exhibit enhanced cellulose dissolution, whereas systems with positive linear increase of α (Lewis acidity) or π (polarizability) values demonstrate improved solubility toward kraft lignin, such as ethylene glycol-based DES.⁹⁴

Acidity

Acidity significantly impacts DES-based phytochemical extraction, as the stability and solubility of the compound often depend on the pH. Alkaloids, for example, are more soluble in acidic media due to protonation,⁹⁵ while anthocyanins are stable at pH 1–3 but degrade under alkaline conditions. Acidic DESs—particularly those using carboxylic acids as HBDs—are widely applied for anthocyanin recovery, with lactic acid often outperforming polycarboxylic acids such as citric or malic acids due to reduced steric hindrance and improved molecular interactions.⁹⁶ Acidic systems can also weaken pectin and hemicellulose, facilitating cell wall disruption and delignification.⁹⁷

In anhydrous DESs, acidity cannot be directly measured by the pH scale; alternative approaches include the Hammett function (*H*₀), p*K*_a determination, organic indicators, conductivity, titration, and computational tools such as Density Functional Theory (DFT).⁹⁸ Moreover, the combination of IR and NMR techniques enables the acidity of DES to be scaled as



seen by Zhou *et al.*⁹⁹ In hydrated DESs, the apparent pH (pH*) can be measured, with values strongly influenced by the type and ratio of HBA to HBD. Sugar- and diol-based DESs tend toward neutral/basic pH*, while carboxylic acid-based systems are highly acidic.⁸¹

Anthocyanin extraction studies confirm the advantage of acidic DESs. From grape skins, ChCl:oxalic acid and ChCl:malic acid (25% water) yielded 18.3 and 14 mg g⁻¹ DW, respectively, outperforming less acidic systems such as ChCl:sorbose or ChCl:glycerol.¹⁰⁰ Similarly, in mulberry extraction, ChCl: citric acid:glucose 1:1:1 molar ratio with 30% water achieved 6.05 mg g⁻¹ FW—1.24 × higher than ethanol, while other organic acids, polyols, and sugars yielded progressively less.¹⁰¹ The higher efficiency of acidic DESs is linked to anthocyanins remaining as the red flavylium cation at pH 1, whereas higher pH values favor quinoidal, colorless, or degraded forms.

Surface tension

Surface tension is a key parameter in phytochemical extraction, influencing solvent–plant interactions, mass transfer, and cell penetration. Low surface tension facilitates spreading over plant surfaces, thereby improving contact and enhancing the release of phytochemicals. In DESs, surface tension depends on HBA–HBD intermolecular forces, molar ratio, viscosity, temperature, and water content. Typically, strong hydrogen bonding networks yield higher surface tension; however, this decreases when tuning the HBD–HBA and their molar ratio. For instance, increasing the alkyl chain length of the HBA cation reduces the surface tension.¹⁰² As seen previously, higher ChCl:glycerol molar ratios also reduce surface tension, whereas HBDs with multiple hydroxyl groups increase it. Among polyols, longer-chain species, such as 1,6-hexanediol, exhibit higher surface tension than glycerol, butanediol, or ethylene glycol.¹⁰³

A comprehensive investigation into the surface tension of 50 DES revealed that the molar ratio and type of HBD significantly influence the surface tension, with a notable increase observed upon water addition (≥0.9 mol ratio), due to the dilution of DES components in water. The DES with the maximum surface tension was ChCl:phytic acid at a 1:2 molar ratio, with a surface tension of 70.5 mN m; however, with mild heating (60 °C), the surface tension decreased in the system. Overall, the glycerol as HBD increases the hydrogen bonding, resulting in an increase in surface tension. As for HBA, the Cl⁻ in ChCl enhances the surface tension compared with other anions like Br⁻ and I⁻.¹⁰⁴ Strong hydrogen-bonding DESs—typically involving polyhydroxylated HBDs and highly electronegative or metal-based HBAs—show higher surface tension and better penetration of lignocellulosic matrices, enhancing the release of bound phytochemicals, whereas weaker hydrogen-bond networks favor gentler and more selective extraction.¹⁰⁴

Effect of water added (ternary systems and beyond)

Water addition is a common strategy to tune the thermophysical and physicochemical properties of the DES, including

melting point, density, viscosity, polarity, and acidity. Controlled incorporation, typically in the range of 20 to 42 wt% (depending on the eutectic system), alters the inter- and intramolecular hydrogen-bond network, enhancing mass transfer and reducing viscosity and surface tension, but potentially weakening hydrogen bonding.¹⁰⁵ Distinguishing between bound and free water is essential, as hydration can also shorten preparation time, lower processing temperatures, and prevent salt crystallization. With sufficient water, viscosity can approach that of pure water, and polarity can be effectively adjusted,¹⁰⁶ at the expense of transitioning to aqueous dilution of the DES components, HBD and HBA.

Water in DESs enhances plant tissue hydration, improving penetration into vacuoles and cytoplasm, and facilitating the release of phytochemicals, thereby mimicking natural metabolite transport.¹⁰⁷ Response surface methodology (RSM) studies indicate that 20–30 wt% water often optimizes flavonoid and polyphenol extraction. Examples include pigeon pea roots (genistin, genistein, apigenin), *Pyrola incarnata* (phenolics), *Cajanus cajan* leaves (phenolics), *Lycium barbarum* fruits (flavonoids), mulberry leaves (phenolics), and tartary buckwheat hull (rutin).¹⁰⁸ Similar ranges (10–40 wt%) have been applied to cumin and *Angelica sinensis* essential oils, artemisinin, boldine, and galanthamine.¹⁰⁹

Optimal hydration depends on DES viscosity and plant matrix. Solid HBDs (*e.g.*, sugars, carboxylic acids) require more water to lower viscosity, while liquid HBDs (*e.g.*, diols) need less. For example, ChCl:oxalic acid:ethylene glycol (50% water) extracted flavonols (quercetin, myricetin, kaempferol), whereas flavanones and other flavonoids typically require 0–40% water.¹⁰² Xu *et al.*⁶⁴ found that adding 20% water to a ChCl:levulinic acid:*N*-methyl urea molar ratio of 1:1.2:0.8 maximized flavonoid yield (56.84 mg g⁻¹), while higher hydration decreased efficiency. The distinction between hydrated DESs and aqueous HBA–HBD solutions is system-dependent. For ChCl:urea, a water content of greater than 51 wt% water disrupts the eutectic structure, yielding a “DES-in-water” system.¹⁰⁵ In ChCl:EG or ChCl:glycerol systems, this transition occurs at ~35 wt% water.¹¹⁰

Types of phytochemicals extracted from agro-food wastes by DESs and their bioactivities

Flavonoids and phenolic acids

Phenolic compounds are secondary metabolites with diverse bioactivities, among which flavonoids stand out for their antioxidant properties. Over 10 000 flavonoids have been identified, all sharing a 15-carbon skeleton with two aromatic rings (A and B) linked by a three-carbon bridge forming an oxygenated heterocycle (ring C).¹⁰² DESs have been widely applied to extract phenolic compounds from plant matrices and food by-products, as illustrated in Table 4.

These extracts, valued for their antioxidant activity against free radicals and reactive oxygen species (ROS), are primarily used in human health applications. From a sustainability





Table 4 Phenolic compounds extracted from agro-food wastes using DES^a

Plant material	Phenolic compound	DES	Extraction-assisted method	Extraction efficiency	Quantification method	Bioactivity	Ref.
Sunflower meal	Chlorogenic acids	Lactic acid : glucose 5 : 1	Ultrasound	1786 mg L ⁻¹	HPLC-PDA	Antioxidant	114
Raw mango peel	TPC	Glycerol : sodium acetate 3 : 1 with 20% water	Microwave	155.28 mg GAE g ⁻¹ DW	Spectrophotometry UV-vis	Antioxidant	115
Bell pepper biomass	Cynaroside and quercitrin	ChCl : 1,6 hexanediol 1 : 1 with 30% water	Ultrasound	Quercitrin: 14.54 µg g ⁻¹ DW Cynaroside 14.14 54 µg g ⁻¹ DW	UPLC-MS/MS	Antioxidant	48
Persimmon calyx	TPC	ChCl : lactic acid 1 : 1.9 with 70% water	Ultrasound	206.13 mg GAE g ⁻¹ DW	Spectrophotometry UV-vis	Antioxidant	116
<i>Citrus aurantium</i> L. peel	TPC	ChCl : 1,4-butanediol 1 : 3 with 49.95% water	Ultrasound	7.85 mg GAE g ⁻¹ DW	Spectrophotometry UV-vis	Antioxidant	117
Apple pomace	TPC	Glucose : fructose : water 1 : 1 : 11	Ultrasound	9.47 mg GAE g ⁻¹	Spectrophotometry UV-vis	Antioxidant	118
Spent coffee grounds	A mixture of derivatives of chlorogenic acids	1,6-Hexanediol : ChCl 7 : 1	Ultrasound	18 mg of 3-caffeoylquinic acid equivalent g ⁻¹	UHPLC Q-TOF-MS	Antioxidant	119
Grape pomace	Total anthocyanins	ChCl : citric acid 2 : 1 with 30% water	Simultaneous ultrasound/microwave	1.77 mg of malvidin-3-O-monoglucoside equivalent g ⁻¹ DW	HPLC-DAD	Not studied	120
By-products of Turkish hazelnut	D-(−)-quinic acid, gallic acid, protocatechuic acid, 4-hydroxybenzoic acid, catechin, caffeic acid, vanillic acid, epicatechin gallate, ferulic acid, sinapic acid, rutin, quercetin-3-O-glucoside, salicylic acid, quercetin-3-O-rhamnoside, quercetin	ChCl : 1,2-propylene glycol 1 : 4 with 25% water	Microwave	A sum of phenolic compounds: 292.36 mg kg ⁻¹ DW	UPLC-PDA-ESI-MS/MS	Antioxidant	121
Black bean hulls	Anthocyanins: delphinidin-3-O-glucoside, malvidin-3-O-glucoside, petunidin-3-O-glucoside	ChCl : citric acid 1 : 1 with 10% water	High-pressure fluid	A sum of anthocyanins: 8.97 mg g ⁻¹ DW	LC/MS-MS	Antioxidant	122
Pomegranate peel waste	TPC	ChCl : lactic acid 1 : 1 with 20% water	Ultrasound	6.4 ± 0.1 mg GAE per mL	Spectrophotometry UV-vis	Not studied	123



Table 4 (Contd.)

Plant material	Phenolic compound	DES	Extraction-assisted method	Extraction efficiency	Quantification method	Bioactivity	Ref.
<i>Hibiscus sabdariffa</i> L. calyces	Anthocyanins (delphinidin-3-sambubioside, cyanidin-3-sambubioside). Flavonoids (myricetin-3-arabinogalactoside, quercetin-3-sambubioside, quercetin-3-rutinoside, kaempferol-3-O-sambubioside, quercetin-3-glucoside, methylpivallocatechin, myricetin, quercetin, kaempferol). Phenolic acids (chlorogenic acid, quinine, neochlorogenic acid, chlorogenic acid, cryptochlorogenic acid, coumaroylquinic acid, 5-O-caffeoyl-shikimic acid)	ChCl : oxalic acid 1 : 1	Microwave	A sum of anthocyanins $7.36 \pm 0.06 \text{ mg g}^{-1} \text{ DW}$ A sum of flavonoids $4.57 \pm 0.12 \text{ mg g}^{-1} \text{ DW}$ A sum of flavonoids and phenolic acids $19.94 \pm 0.60 \text{ mg g}^{-1} \text{ DW}$	HPLC-ESI-TOF-MS	Not studied	124
	Flavan-3-ols (catechin, epicatechin, gallic acid, catechin gallate, epicatechin gallate, procyanidin B1, procyanidin B2, procyanidin B4, galloylated dimers, monomer glycosides. Stilbenes (t-resveratrol glucoside, c-resveratrol glucoside). Flavonols (myricetin-3-glucuronide, myricetin-3-glucoside, quercetin-3-galactoside, quercetin-3-glucuronide, quercetin-3-glucoside, lutein-3-glucoside, kaempferol-3-glucoside, isorhamnetin-3-glucoside, syringetin-3-glucoside)	ChCl : urea 1 : 2 with 30% subcritical water	Subcritical water	A sum of flavan-3-ols $1763.53 \pm 46.83 \text{ } \mu\text{g g}^{-1} \text{ DW}$ A sum of stilbenes $1.20 \pm 0.13 \text{ } \mu\text{g g}^{-1} \text{ DW}$. A sum of flavonols $139.42 \pm 0.70 \text{ } \mu\text{g g}^{-1} \text{ DW}$	HPLC-DAD-ESI-MSn	Antioxidant	125
Winemaking by-products	Phenolic acids (ellagic acid, gallic acid, ferulic acid). Flavonols (myricetin, quercetin, kaempferol). Flavan-3-ols (catechin, epicatechin)	ChCl : levulinic acid : ethylene glycol 1 : 1 : 2 with 20% water (DES1) ChCl : proline : malic acid 1 : 1 : 1 with 30% water (DES2)	Ultrasound	Grape skin (sum of phenolic compounds obtained by DES1, $40.7 \text{ mg g}^{-1} \text{ DW}$) Grape seeds (sum of phenolic compounds obtained by DES2, $3.87 \text{ mg g}^{-1} \text{ DW}$)	HPLC	Not studied	126

Table 4 (Contd.)

Plant material	Phenolic compound	DES	Extraction-assisted method	Extraction efficiency	Quantification method	Bioactivity	Ref.
Orange peel waste	Gallic acid, ferulic acid, and <i>p</i> -coumaric acid	ChCl : ethylene glycol 1 : 4	Maceration	Gallic acid: 0.847 mg GAE g ⁻¹ DW. Ferulic acid: 2.42 mg GAE g ⁻¹ DW. <i>p</i> -coumaric acid: 2.29 mg GAE g ⁻¹ DW	RP-HPLC	Antioxidant	127
Olive leaves	Hydroxytyrosol	Citric acid : glycine : water 2 : 1 : 1	Ultrasound	87 ppm	HPLC-UV	Not studied	73
Olive pomace	Oleuropein, hydroxytyrosol, caffeic acid, vanillin, rutin, luteolin	ChCl : citric acid 1 : 2 with 20% water	Homogenate (H), microwave (M), ultrasound (U), high hydrostatic pressure (HHP)	A sum of phenolic compounds H: 18.30 ± 0.18 mg g ⁻¹ DW. M: 6.51 ± 0.04 mg g ⁻¹ DW. U: 2.51 ± 0.02 mg g ⁻¹ DW. HHP 1.99 ± 0.01 mg g ⁻¹ DW	HPLC-DAD	Antioxidant	128
Cocoa by-products	Catechin, procatechuic acid, procyanidins B2	Betaine : glucose 1 : 1	Ultrasound	A sum of phenolic compounds: 7 mg g ⁻¹ DW	HPLC	Antioxidant	129
Waste chestnut shell	Ellagic acid	ChCl : <i>n</i> -propanol 1 : 1	Ultrasound	4.64 mg g ⁻¹ DW	RP-HPLC	Antioxidant, antibacterial activity against <i>S. aureus</i> , <i>B. subtilis</i> , <i>P. aeruginosa</i> , <i>E. coli</i> , <i>C. albicans</i> , and <i>Enterococcus faecium</i>	130
Olive oil processing wastes	Oleuropein, 3,4-DHPEA-EA, hydroxytyrosol, oleacein, demethyloleuropein	ChCl : glycerol 1 : 1 with 20% water	Microwave	Oleuropein: 88 287.57 ± 0.24 ppm, 3,4-DHPEA-EDA: 480.60 ± 0.55 ppm, demethyloleuropein 1019.84 ± 0.53 ppm	HPLC	Antioxidant	131
Mangrosten peel	Proanthocyanidin total content	ChCl : lactic acid 1 : 2	Ultrasound	37 638 ± 6389 mg epicatechin equivalent per 100 g	Spectrophotometry UV-vis	Antioxidant	132
Hazelnut skin	TPC	ChCl : lactic acid 1 : 2 with 35% water	Ultrasound	16.80 g GAE per 100 g DW	Spectrophotometry UV-vis	Not studied	133
Black rice bran	Total anthocyanin content	Lactic acid : fructose 5 : 1	Ultrasound	109.68 mg L ⁻¹	Spectrophotometry UV-vis	Not studied	134
Coffee by-products	Chlorogenic acid	Lactic acid : ChCl 2 : 1 with 10% water	Ultrasound	Chlorogenic acid 0.41 ± 0.002 g per 100 g DW	HPLC	Not studied	135
Avocado peels	Catechin, 3,4 hydroxybenzoic acid, 2,5 hydroxybenzoic acid, gallic acid, epicatechin, ferulic acid, rutin	Acetic acid : ChCl : water 1 : 1 : 10	Maceration	A sum of phenolic compounds 829 mg per 100 g DW	HPLC-DAD	Antioxidant, antibacterial against <i>Staphylococcus aureus</i> ,	136





Table 4 (Contd.)

Plant material	Phenolic compound	DES	Extraction-assisted method	Extraction efficiency	Quantification method	Bioactivity	Ref.
Cocoa bean shell	Catechin and caffeic acid	ChCl : oxalic acid 1 : 1 with 50% water	Microwave	Catechin: 0.0654 mg g ⁻¹ DW, caffeic acid: 0.137 mg g ⁻¹ DW	HPLC-DAD	<i>Streptococcus dysgalactiae</i> , <i>Escherichia coli</i> , and <i>Pseudomonas putida</i> Antioxidant	137
Defatted raspberry seeds	Ellagic acid	Citric acid : betaine 3 : 1 with 25% water	Ultrasound	147.02 ± 7.18 mg per 100 g DW	HPLC-DAD	Anti-proliferative activity (HT29 cells), antioxidant	138
Onion solid waste	Quercetin 4'-O-glucoside, quercetin	Glycerol : sodium propionate 8 : 1	Maceration	Quercetin 4'-O-glucoside: 47.41 µg mL ⁻¹ , quercetin: 64.40 µg mL ⁻¹	LC-DAD-MS	Antioxidant	139
Saffron processing wastes	Flavonols (kaempferol 3-O-sophoroside 7-O-glucoside, quercetin 3-O-sophoroside, kaempferol 3-O-sophoroside, kaempferol 3-O-glucoside). Anthocyanins (delphinidin 3,5-di-O-glucoside, petunidin 3,5-di-O-glucoside, delphinidin 3-O-glucoside)	L-lactic acid : glycine 5 : 1 mol ratio with 20% water	Maceration	A sum of flavonols: 45.72 mg g ⁻¹ , a sum of anthocyanins: 8.06 mg g ⁻¹	HPLC-DAD	Antioxidant	140

^a DW (dry weight).

perspective, valorizing food waste and by-products as nutraceuticals or antioxidant additives increases their economic value and aligns with the growing demand for natural ingredients in functional foods.¹¹¹ The solubility of flavonoids and phenolic acids in protic DESs is enhanced by structural features such as phenolic, gallol, and catechol groups, along with acidic protons; thus, acidic, polyol-, and sugar-based DESs are particularly suited for their extraction.⁵¹

Selected examples have demonstrated the superior performance of DES in extracting phenolic compounds from food by-products and waste biomass. Walnut (*Juglans regia* L.) shells are rich in phenolic acids and flavonoids, representing a valuable source for valorization. DES formulations based on ChCl: glucose (2 : 1, molar ratio) and ChCl: glycerol (1 : 2), each containing 30% v/v water and assisted by ultrasound, achieved the highest total phenolic content (TPC) extractions (41.0 ± 5.2 g GAE kg⁻¹). Among all solvents tested, these DES offered superior protection of phenolics, retaining higher concentrations after simulated gastric (34.9 ± 1.6 g GAE kg⁻¹) and intestinal digestion (27.1 ± 1.6 g GAE kg⁻¹), consistently outperforming ethanol. In contrast, a 1 : 2 ChCl: lactic acid DES produced the greatest flavonoid bioaccessibility ($\approx 80\%$) while preserving antioxidant activity. LC quantification further showed that the maximum phenolic acid bioaccessibility—approaching 100%—was achieved with extracts obtained using ChCl: glycerol. Overall, the study demonstrates that DES not only enhances extraction efficiency but also improves gastrointestinal bioaccessibility of phenolic compounds, underscoring their potential for nutraceutical and functional food applications.¹¹²

Similarly, among various DES evaluated and conventional extracts, ChCl: fructose 1 : 1 molar ratio containing 30% v/v water, assisted by microwave irradiation, achieved the highest TPC from walnut green husk, reaching 85 mg GAE g⁻¹ DW. This performance is attributed to the higher polarity, mild acidity, and moderate viscosity of the DES. Single-factor experiments indicated that increasing the molar proportion of ChCl enhanced extractability; however, no statistically significant differences in antioxidant capacity were observed across molar ratios. The addition of 30% water improved both TPC and antioxidant activity, although these parameters gradually decreased at higher water contents (50–60%), as dilution of the HBD and HBA occurs. Microwave power also played a role, with 350 W delivering the most favorable extraction outcomes. After optimization, the best overall conditions were identified as 36.70% water, a liquid-to-solid ratio of 52.387 mL g⁻¹, and a temperature of 49.9 °C. SEM micrographs of plant tissues further revealed that DES actively disrupts the cell wall through cellulolytic mechanisms, facilitating the release of intracellular phenolic compounds.¹¹³

Terpenes

Terpenes, the most abundant and structurally diverse phytochemicals, are composed of isoprene units (C₅H₈) and classified by unit number into hemiterpenes, monoterpenes, sesquiterpenes, diterpenes, triterpenes, tetraterpenes, and polyterpenes. They are biosynthesized *via* the mevalonate pathway, with

mevalonic acid as a key intermediate.¹⁴¹ Hydrophobic type V DESs are particularly suited for extracting these nonpolar metabolites, mainly carotenoids (tetraterpenes) (Table 5).

Selected examples of DES for terpene extraction are shown below. Terpene trilactones from *Ginkgo biloba* leaves have been obtained using a triphasic DES system 35 : 5 : 40 v/v composed of —ChCl: levulinic acid (1 : 2 molar ratio, 40 wt% water), ChCl: malonic acid (1 : 2 molar ratio, 55 wt% water), and methyl-trioctyl ammonium chloride : capryl alcohol : octylic acid (1 : 2 : 3 molar ratio)—yielding 22.86 ± 0.06 mg g⁻¹.¹⁴² Medicinal triterpenic acids, including ursolic, oleanolic, and betulinic acids, were extracted from *Eucalyptus globulus* bark using menthol: thymol 1 : 2 molar ratio, achieving up to 2.9 wt% ursolic acid per biomass weight.¹⁴³ On the other hand, terpenoids from celery leaves have been successfully extracted using DESs coupled with microwave or ultrasound assistance. After process optimization, the predicted microwave-enhanced conditions consisted of a sample-to-solvent ratio of 0.019 g mL⁻¹, 10% water content, 86 W of microwave power, and a 4 min extraction time, yielding 56.22 mg ursolic acid (UA) equivalents g⁻¹ DW. Under ultrasound processing, optimal extraction was achieved at a sample-to-solvent ratio of 0.018 g mL⁻¹, a water content of 10.6%, an extraction temperature of 37 °C, 18.71 min of sonication, and an ultrasonic power of 416.22 W, resulting in 76.22 ± 0.712 mg UAE g⁻¹ of total terpenoid content. Notably, both extraction strategies employed the same DES system—acetic acid: glucose at a 2 : 1 molar ratio—indicating that the choice of energy-assisted technique substantially influences the efficiency of terpene recovery from plant matrices.¹⁴⁴

Essential oils are highly valued across multiple industrial sectors, and DESs offer a sustainable and efficient alternative for extraction. For example, following a COSMO-RS screening of 2040 DES prepared from 34 HBAs and 60 HBDs in equimolar proportions (1 : 1), a hydrophobic DES composed of menthol: camphor was identified as the most effective solvent, recovering 17.71 mg g⁻¹ of limonene from pomelo peel—94.38% higher than *n*-hexane. According to the authors, DES derived from terpenes and long-chain fatty acids exhibited the highest limonene solubility, whereas those formed from sugars and amino acids showed reduced affinity. This behavior is governed by the infinite-dilution activity coefficient (γ^∞), where lower values indicate stronger interactions between the DES and the solute. In this context, the enhanced solubility of limonene results from extensive van der Waals interaction surfaces between the DES constituents and limonene, creating a more favorable thermodynamic environment for solute incorporation.¹⁴⁵ Conversely, a ChCl: oxalic acid DES significantly enhanced the extraction of essential oil from *Citrus maxima* peel, which is rich in β -myrcene (38%), α -limonene (37%), and β -pinene (4.3%). Following process optimization, the optimal conditions consisted of a homogenization time of 54.38 s, a liquid-to-material ratio of 4.99 mL g⁻¹, and an extraction pH of 3, resulting in an essential oil yield of 14.28 ± 0.16 mL kg⁻¹ DW. This formulation demonstrates that acidic DES can effectively disrupt plant matrices and enhance terpenoid recovery, offering a promising alternative to conventional organic solvents.¹⁴⁶ As expected, several types of HBAs and





Table 5 Terpenes extracted from agro-food wastes using DES^a

Source	Terpene	DES	Extraction-assisted method	Extraction efficiency	Quantification-identification method	Bioactivity	Ref.
Tomato skin waste	Lycopene	Menthol : thymol 1 : 1	Ultrasound	484.2 mg g ⁻¹ dry extract	HPLC-DAD	Not studied	148
Pumpkin peels	Total carotenoids	ChCl : triethylene glycol 1 : 3	Ultrasound	2.460% ± 0.037% yield	Spectrophotometry UV-vis	Antioxidant <i>in vitro</i> e amylase inhibitory	149
Tomato fruits	Lycopene	Capric acid : lauric acid 1 : 2	Maceration	15.04 ± 0.34 mg per 100 g FW	RP-HPLC-DAD	Not studied	150
Shrimp head by-product	Astaxanthin	ChCl : L(+)-tartaric acid 2 : 1 with 20% MeOH	Ultrasound, microwave	Ultrasound: 7.85 ± 2.3 mg per 100 g DW. Microwave: 26.7 ± 2.5 mg per 100 g DW.	Spectrophotometry UV-vis	Antioxidant	151
Shrimp wastes	Astaxanthin	ChCl : lactic acid 1 : 2 with 10% water	Ultrasound	68.98 ± 1.22 mg g ⁻¹	HPLC/UV-vis	Antioxidant	152
Pumpkin	β-carotene	Caprylic acid : capric acid 3 : 1	Ultrasound	51.41 µg mL ⁻¹	HPLC/UV-vis	Not studied	153
Orange peel	Total carotenoids	DL-menthol : camphor 1 : 1	Maceration	163.5 ± 1.1 mg per 100g FW	Spectrophotometry UV-vis	Antioxidant, antiproliferative in HeLa cells	154
Crab shell residues	Astaxanthin	Menthol : myristic acid 8 : 1	Stirring	9.3 ± 0.8 µg g ⁻¹ DW	HPLC-UV/vis	Antiproliferative in HT-29 cells, antibacterial against <i>S. aureus</i> and <i>E. coli</i>	155
Shrimp shells	Astaxanthin	Lysine : citric acid 1 : 2 with 30% water	Ultrasound	112.80 µg g ⁻¹	Spectrophotometry UV-vis	Not studied	156

^a FW (fresh weight), DW (dry weight).

HBDs, such as carboxylic acids, sugars, and polyols, can be useful for extracting essential oils; this capability is not unique to HDES. This is due to the varied types of molecules, *i.e.*, monoterpenes, sesquiterpenes, aldehydes, alcohols, ketones, esters, *etc.*, present in essential oils, which vary their polarity, acidity, and physicochemical properties, as well as the plant matrix structure, which plays a pivotal role in DES selection.¹⁴⁷

Alkaloids

Alkaloids are nitrogen-containing secondary metabolites of notable medicinal value, historically used and still serving as precursors for many modern drugs. Derived mainly from amino acids, they exhibit diverse bioactivities, including antiviral, antibacterial, antitumoral, insecticidal, antifungal, anti-inflammatory, antioxidant, and antidiabetic effects.¹⁵⁷

Although agricultural wastes and food by-products generally contain low concentrations of alkaloids, several studies have demonstrated that DES are effective in recovering these compounds (Table 6). For example, a lactic acid : glucose 5 : 1 molar ratio efficiently recovered theophylline, piperine, and harmaline from *Larrea divaricata*, outperforming methanol and water.¹⁵⁸ Moreover, DESs can enhance alkaloid bioavailability; solubilizing berberine in a proline : malic acid : lactic acid : water 1 : 0.2 : 0.3 : 0.5 molar ratio increased blood concentrations 2–20-fold compared to aqueous berberine, significantly improving pharmacokinetics.¹⁵⁹

Conversely, after screening 30 different DES formulations, L-proline : 1-methylurea (1 : 2.8 molar ratio) with 39.8% alkaline electrolyzed water demonstrated superior performance, outperforming ultrasound-assisted DES and conventional solvents in the extraction of total alkaloids (liensinine, isoliensinine, and neferine) from *Nelumbinis plumula*, achieving 16.97 mg g⁻¹ under optimized conditions (pH 12.8 and a pretreatment time of 8.5 min). The authors reported that alkaline DES markedly enhanced alkaloid recovery, whereas acidic HBAs and HBDs produced the opposite trend. Molecular dynamics simulations elucidated the extraction mechanism, revealing a strong hydrogen-bonding capacity between methylurea and polar moieties, as well as extensive van der Waals interactions at the DES-alkaloid interface. Furthermore, the addition of water to the system promoted hydrogen-bond formation not only between the HBA and HBD but also between the DES and the polar groups in alkaloids, thereby facilitating molecular solvation and enhancing extraction efficiency.¹⁶⁰

Similarly, among 18 DES evaluated, the ChCl : formic acid system 1 : 2 molar ratio containing water (mass ratio 5 : 5) was identified as the most effective DES for extracting the bioactive indole alkaloids camptothecin, 10-hydroxycamptothecin, and vincosamide from *Camptotheca acuminata*. Optimal extraction conditions were achieved at a solid-to-liquid ratio of 1 : 80 g mL⁻¹, an ultrasonic power of 360 W, an extraction temperature of 70 °C, and an ultrasonic time of 50 min, resulting in a total alkaloid yield of 0.73%. DFT calculations revealed that the interaction energy between camptothecin and the DES reached -16.32 kcal mol⁻¹, indicating strong molecular affinity. These calculations support the high extraction efficiency by

demonstrating stable hydrogen-bond networks mediated by the carboxylic moiety of formic acid and favorable solvation environments.¹⁶¹

Saponins

Saponins are glycosylated secondary metabolites comprising a hydrophobic aglycone (sapogenin, C₂₇–C₃₀) linked *via* C–O-sugar bonds to one or two sugar moieties, forming the hydrophilic portion. Bioactivity is largely determined by the type of aglycone. The most common are triterpenoid glycosides (>60 types), which can be bidesmosidic (two sugars), monodesmosidic (one sugar), steroidal (steroidal aglycone + one sugar), or alkaloid saponins (alkaloid aglycone + one sugar).¹⁶⁹ Applications include roles as emulsifiers, stabilizers, and foaming agents in the food industry, and as drug-release agents, precursors for steroidal drugs, or APIs in pharmaceuticals. Medicinal activities encompass antioxidant, antidiabetic, *anti-obesogenic*, anti-inflammatory, antiviral, antibacterial, anticancer, antitumor, and antihypertensive effects.¹⁷⁰ Saponins are widely distributed in grains, seeds, and legumes (such as soybeans, peanuts, kidney beans, broad beans, and chickpeas) and are abundant in plants like green tea, spinach, sugar beets, yucca, tomatoes, asparagus, and peppers. Although DES-based extraction from agricultural waste and food by-products remains limited, studies report high yields from medicinal and edible plants (Table 7).

For example, tea saponins from *Camellia oleifera* shells have been successfully extracted using a L-proline:acetamide at a 1 : 4 molar ratio with 30% water. After process optimization (liquid-solid ratio of 24 mL g⁻¹, extraction time of 47 min, and extraction temperature of 81 °C), the DES achieved an extraction efficiency of 22.46%. The authors noted that weakly acidic DES significantly improves saponin recovery, whereas strongly acidic DES has the opposite effect. Notably, the DES outperformed conventional solvents, achieving yields 1.6 times higher than those of water and 1.3 times higher than those of 80% ethanol. These results suggest that tea saponins display superior solubility in weakly acidic protic DES, compared with those formulated using lactic acid, glycerol, or ethylene glycol.¹⁷¹

Conversely, after screening 43 DES formulations, the ChCl:urea system (1 : 2 molar ratio) was identified as the most effective solvent for extracting ginsenosides (106.8 mg g⁻¹), a class of dammarane-type triterpene saponins, from *Panax notoginseng* leaves. Process optimization yielded the optimal extraction parameters at a water content of 29.1%, a solid-to-liquid ratio of 1 : 50.9, an extraction temperature of 50.8 °C, and an extraction time of 59.2 min. In addition to achieving higher extraction yields, the DES markedly reduced ginsenoside hydrolysis (7%) compared to conventional water extraction (100%). DFT and molecular dynamics simulations further elucidated the extraction mechanism, revealing that the DES promotes strong electrostatic potential interactions with ginsenosides, exhibits low binding energies, and forms balanced and effective hydrogen-bonding networks and van der Waals interactions. These molecular interactions stabilize the dammarane core and glycosidic moieties, thereby enhancing extraction efficiency while preserving structural integrity.¹⁷²





Table 6 Alkaloids extracted from agro-food wastes using DES

Plant material	Alkaloid	DES	Extraction-assisted method	Extraction efficiency	Quantification-identification method	Bioactivity	Ref.
<i>Nicotiana tabacum</i> leaf waste	Total alkaloids (nicotine)	ChCl : urea : water 1 : 2 : 1.5	Maceration	1123.0 ± 7.0 µg mL ⁻¹	Spectrophotometry UV-vis	Antioxidant	162
Raw coffee beans	Caffeine, trigonelline	Aqueous solution of ChCl (50% v/v)	Ultrafast rotary disintegrator/homogenizer	Caffeine: 147.7 ± 0.7 g per 100 g Trigonelline: 117.6 ± 1.3 g per 100 g	HPLC-DAD	Antioxidant	163
<i>Evodia leptostachya</i> root residue	Skimmianine, dictamnine, evodiamine	Levulinic acid:glycerol 1.5 : 1 containing 30% K ₂ HPO ₄ solution	Microwave	A sum of alkaloids: 57.71 µg g ⁻¹	HPLC-UV/vis	Not studied	164
<i>Peumus boldus</i> leaves	Boldine	l-proline : oxalic acid 1 : 1 with 20% water	Ultrasound	2.362 ± 0.055 mg g ⁻¹	HPLC-DAD-IT/MS	Not studied	165
<i>Camelia sinensis</i> leaves	Caffeine and theobromine	ChCl : 1,4-butanediol 1 : 3 with 50% water	Mechanochemical	Caffeine: 21.8727 ± 0.22994 mg g ⁻¹ Theobromine: 0.3423 ± 0.00352 mg g ⁻¹	UPLC-MS	Not studied	166
<i>Phellodendron amurense</i> cortex	Berberine, palmatine	ChCl : citric acid 1 : 2 with 70% water	Ultrasound	Berberine 9.64 mg g ⁻¹ Palmitine 4.26 mg g ⁻¹	HPLC-UV/vis	Antioxidant	167
<i>Areca catechu</i> seeds	Arecoline, arecaine, guvacoline, guvacine	Proline : lactic acid 1 : 2	Ultrasound	A sum of alkaloids 52.99 ± 1.05 mg g ⁻¹ DW	HPLC-DAD	Antioxidant α -glucosidase inhibitory activity, anti-bacterial activity against <i>Listeria monocytogenes</i> , <i>S. aureus</i> , <i>Bacillus subtilis</i> , <i>E. coli</i> , <i>S. Typhimurium</i> , <i>P. aeruginosa</i>	168



Table 7 Saponins extracted from agro-food wastes using DES

Plant material	Saponins	DES	Extraction-assisted method	Extraction efficiency	Quantification-identification method	Bioactivity	Ref.
<i>Chenopodium quinoa</i> Willd. Husks	Total saponins	ChCl : 1,2-propylene glycol 1 : 1 with 40% water	Ultrasound	53.72 ± 0.1 mg g ⁻¹ DW	Spectrophotometry UV-vis	Antioxidant	173
<i>Agave sisalana</i> and <i>Ziziphus joazeiro</i>	Total saponins	<i>Agave</i> : ChCl : propionic acid 2 : 1 with 19% water <i>Ziziphus</i> : ChCl : phenylacetic acid 2 : 1 + ethanol solution 42% L-proline : glycerol : Sucrose 1 : 10 : 1	Maceration	<i>Agave</i> : 245% extraction efficiency <i>Ziziphus</i> : 170% extraction efficiency	Spectrophotometry UV-vis	Not studied	174
Seed pomace of <i>Camellia oleifera</i>	Assamsaponin I, C, D, A, E, camelliasaponin B2, camelliasaponin A2, C2, oleanolic acid 3-O-beta-D-glucosiduronic acid, gypsogenin		Ultrasound	Total saponins yield: 23.22 ± 0.28%	Identification: UHPLC-HF MS Quantification UV-vis	Antioxidant and antimicrobial against <i>S. aureus</i> , <i>E. coli</i> , and <i>C. albicans</i>	175
Husks of <i>Xanthoceras sorbifolia</i> Bunge	Triterpenoid saponins (16-O-acetyl-21-O-α-L-rhamnopyranosyl-β-barringtonenol C, 3-O-β-D-glucopyranosyl, 28-O-[α-L-rhammol (1 → 2)]-β-D-glucopyranosyl-16-deoxybarringtonenol C, 3-O-[β-D-glucopyranosyl (1 → 6)] (3'-O-angeloyl)-β-D-glucopyranosyl-28-O-[α-L-rhamnosyl (1 → 2)]-β-D-glucopyranosyl-16-deoxybarringtonenol C, 3-O-(3-O-angeloyl-4-O-acetyl-6-O-β-D-glucopyranosyl)-β-D-glucopyranosyl-28-O-(2-α-L-rhamnopyranosyl)-6-O-β-D-glucopyranosyl)-β-D-glucopyranosyl-16-deoxybarringtonenol C, xanifoliaY7, and xanifolia Y2, xanthoceracide)	Tetrapropylammonium bromide : lactic acid 1 : 2	Maceration	Total saponins: 72.11 ± 0.61 mg g ⁻¹ DW	Identification: HPLC-ESI-MS Quantification: UV-vis	Antioxidant	176



Table 7 (Contd.)

Plant material	Saponins	DES	Extraction-assisted method	Extraction efficiency	Quantification-identification method	Bioactivity	Ref.
<i>Chenopodium quinoa</i> seeds and husks	Mixture of saponins	ChCl : glycerol : water 1 : 2 : 1	Maceration	Husk of bitter seed: 34 301 ± 1101 µg g ⁻¹ Bitter seed: 3688 ± 20.4 µg g ⁻¹	UPLC-ESI-MS	Not studied	177
<i>Camellia oleifera</i> seed meal	A mixture of tea seed saponins, theasaponins, oleiferasaponins, assamsaponins, floratheasaponins	ChCl : methyl urea 1 : 1 with 20% water	Maceration	Total saponins: 94.36 mg g ⁻¹	Identification: UPLC-Q/TOF-MS Quantification: UV-vis	Not studied	178

General DES-based protocols for phytochemical purification and recovery

Addition of antisolvents and precipitation (solid-liquid and liquid-liquid extraction). In recent years, DESs combined with antisolvents and precipitation methods (solid-liquid and liquid-liquid extraction) have emerged as green and sustainable approaches for phytochemical extraction and purification.¹⁷⁷ Their recyclability is an advantage over conventional organic solvents, but DES recovery is challenging due to their low vapor pressure and physicochemical properties, making evaporation-based separation unsuitable for industrial use.

To recover target compounds and recycle DES, strategies include liquid-liquid extraction with alternative solvents, solid-liquid extraction using macroporous resins, and antisolvent addition.^{75,179} Hydrophilic DES interacts strongly with protic solvents *via* hydrogen bonding, while remaining immiscible with aprotic solvents, enabling selective solubility in liquid-liquid extractions.

Rosarina *et al.*¹⁸⁰ demonstrated that a ChCl : lactic acid DES, combined with the antisolvent *n*-hexane and ultrasonic-assisted extraction, efficiently solubilized curcuminoids from *Curcuma* spp., which subsequently precipitated upon addition of the antisolvent, enabling straightforward recovery. Similarly, ChCl : oxalic acid : KOH has been applied for the environmentally friendly fractionation of cellulose and lignin, where the introduction of acetone induced biomass precipitation from the DES solution.¹⁸¹ ChCl : citric acid proved optimal for selectively isolating isoflavones—genistein, daidzein, genistin, and daidzin—from soy-based food products. In this case, methanol served as the antisolvent to precipitate the target compounds.¹⁸²

Another purification strategy is solid-phase extraction, in which less polar analytes are adsorbed onto resin cartridges. The DES is subsequently washed out with water, and the retained analytes are eluted using an alcoholic solvent such as ethanol.¹⁸³ Using this strategy, Wang *et al.*¹⁸⁴ extracted flavonoids from safflower using a ChCl : ethylene glycol DES coupled with ultrasound-assisted extraction. Likewise, Bi *et al.*,¹⁸⁵ employed a ChCl : lactic acid DES in microwave-assisted extraction to recover anthocyanins and flavonoids from mulberry fruits, followed by direct separation using macroporous resin ME-2, achieving recovery yields of approximately 80–85%.

Aqueous biphasic systems. The integration of DESs into aqueous two-phase systems (ATPS) offers a sustainable alternative to conventional solvent extraction. This approach combines the green chemistry advantages of DESs with the partitioning efficiency of ATPS, eliminating the need for volatile organic solvents and exhibiting low viscosity, minimal emulsion formation, and high biocompatibility.^{186,187}

In one example, raw polysaccharides from *Camellia oleifera* seed cake were extracted using a ChCl : ethylene glycol DES, followed by purification *via* a thermoseparating EOPO-based ATPS. During the first extraction, polysaccharides partitioned into the EOPO-rich phase, yielding 86.91%. A second ATPS step then recovered 84.92% into the aqueous phase, providing an efficient two-step separation.¹⁸⁸ Similarly, bioactive compounds

from dried *Moringa oleifera* leaves were extracted using ChCl:citric acid DES in combination with an ammonium sulfate:ethanol ATPS.¹⁸⁹ Vieira *et al.*¹⁹⁰ further exploited DES tunable polarity and viscosity to design a biphasic system enabling the simultaneous recovery of polar rosmarinic acid and non-polar diterpenes (carnosic acid, carnosol) from *Rosmarinus officinalis*.

Macroporous adsorption resins. The recovery, purification, and enrichment of bioactive compounds from NaDESs remain challenging, as their high solubilization capacity promotes strong retention of solutes within the DES phase, limiting partition efficiency.¹⁹¹ Recovery strategies must account for the physicochemical and thermal properties of the DES, as well as the chemical nature of both the biomass and target phytochemicals. Adsorption-desorption using macroporous resins offers a scalable solution, combining low cost, high adsorption/desorption capacity, mechanical robustness, and facile regeneration.¹⁹² This is particularly relevant given the comparable flavonoid extraction efficiencies achieved by DESs and conventional organic solvents.

For example, recovery of glycyrrhizic acid from a ChCl:lactic acid DES was optimized using DIAION™ SP700 resin (cross-linked polystyrene-divinylbenzene, 10–100 Å pore dimensions, ~1200 m² g⁻¹ surface area), yielding high adsorption/desorption performance.¹⁹³ Similarly, chlorogenic acid was extracted from *Herba artemisiae scopariae* using a proline:malic acid DES with ultrasonic disruption, followed by purification *via* NKA-9 resin (weak-to-moderate polarity, cross-linked polystyrene-divinylbenzene), achieving a yield of 3.77 mg g⁻¹.¹⁹⁴ Flavonoids from oil palm (*Elaeis guineensis*) leaves—agricultural residues from plantations—were recovered using ChCl-based DESs with 1,2-propanediol, 1,4-butanediol, or glycerol as HBDs, followed by separation with XAD7HP resin (nonionic aliphatic acrylic polymer, 550 Å pores diameter, ≥500 m² g⁻¹

surface area), efficiently isolating >12 luteolin and apigenin derivatives.¹⁹⁵ In *Chenopodium quinoa*, flavonoids and 20-hydroxyecdysone were purified from ChCl:urea extracts using D101 resin (cross-linked polystyrene-divinylbenzene, 90–110 Å pore dimensions, 500–600 m² g⁻¹ surface area), enabling both phytochemical recovery and DES removal.¹⁹⁶

Troubleshooting phenolic quantification in DES extracts: Folin-Ciocalteu limitations and alternatives. A persistent limitation in the extraction of phytochemicals using DESs is the precise quantification and characterization of polyphenols, a step often considered a critical bottleneck in the process. High-resolution chromatographic techniques, notably LC coupled with diode-array detection (DAD) or UV, or mass spectrometry (MS), remain the gold standard for phenolic identification and quantification, enabling the generation of detailed compositional profiles with high analytical accuracy.¹⁹⁷ Despite their reliability, these methods require advanced instrumentation and specialized expertise, underscoring their operational complexity. Consequently, colorimetric assays—particularly the Folin-Ciocalteu (F-C) method—are frequently adopted for routine analyses owing to their simplicity, rapidity, and cost-effectiveness.

The F-C assay is a colorimetric redox-based method primarily used to quantify the total phenolic content or the total reducing capacity in organic samples, such as foods, plant extracts, and biological matrices. This method relies on a single-electron transfer reaction between phenolic compounds (or any reducing agents, such as sugars, thiols, proteins, amino acids, and organic acids) and the phosphomolybdic-phosphotungstic acid complex under alkaline conditions.¹⁹⁸

Many DESs employed for polyphenol extraction are acidic, a factor that critically influences the performance of the Folin-Ciocalteu (F-C) assay. Under alkaline conditions, phenolics are deprotonated to phenolate anions, which reduce Mo(VI) and

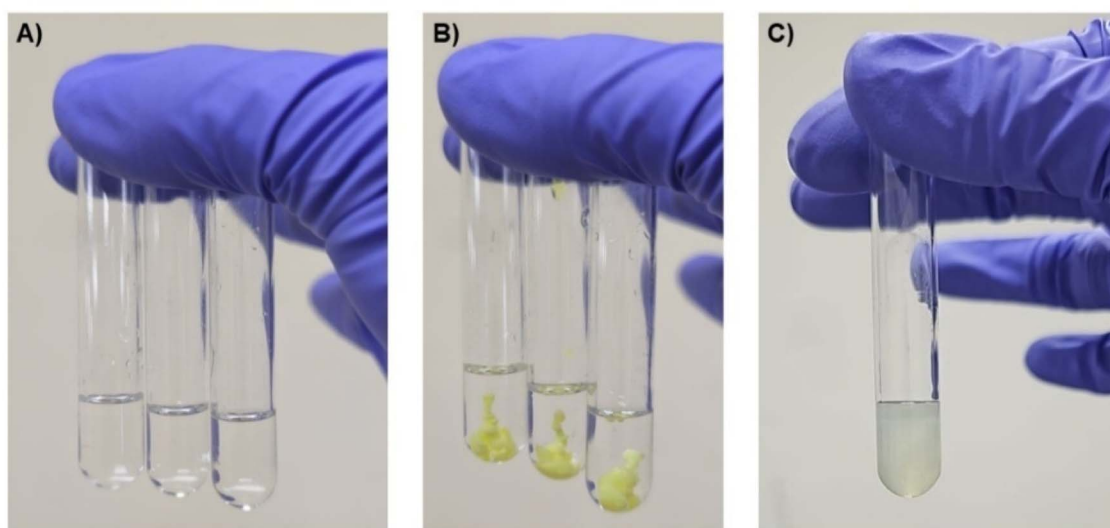


Fig. 5 Yellowish precipitate formed between DES and the Folin-Ciocalteu reagent. (A) DES based on ChCl:lactic acid with different water percentages, 0, 15, and 30 wt%. (B) F-C reagent precipitate in DES. (C) DES with F-C reagent after vortexing, the turbidity is so high that it renders measurement by spectrophotometry impossible.



W(vi) species in the F–C reagent, producing blue mixed-valence molybdenum–tungsten complexes with strong absorbance at 750–765 nm.¹⁹⁹ While widely used for determining total phenolic content, the F–C assay often overestimates results due to limited reagent selectivity and interference from other reducing substrates. This is particularly relevant for DES extracts, as common DES constituents—including polyols, sugars, carboxylic acids, amino acids, quaternary ammonium salts, and variable pH—can react with the reagent, causing inaccurate measurements.²⁰⁰ The assay typically operates at pH $\approx$ 10, adjusted with sodium carbonate, to ensure efficient phenol oxidation; however, acid-based DESs disrupt this environment, generating substantial interference. Conversely, sugar-, amino acid-, and polyol-based DESs may yield inflated values due to intrinsic reducing capacity. Moreover, phosphomolybdate anions can interact electrostatically and *via* hydrogen bonding with quaternary ammonium salts, such as ChCl, destabilizing or prematurely reducing the complex and producing precipitates, turbidity, or erroneous absorbance readings as seen in Fig. 5.²⁰¹

A growing body of research has documented significant analytical interferences when quantifying phenolics in DES extracts using spectrophotometric assays. For instance, Soares *et al.*²⁰⁰ evaluated acidic- and polyol-based ChCl DESs for phenolic extraction from sunflower meal, revealing a strong dependence of quantification on pH and HBD type. The F–C assay systematically overestimated the contents relative to HPLC, whereas the Prussian Blue assay underestimated the content in all DES tested, and the Fast Blue assay underestimated, except in urea- and glycerol-based DESs. None of the colorimetric methods matched the accuracy of HPLC, with all DES producing a yellow insoluble precipitate. Similar F–C reagent interferences have been reported for ChCl:tartaric acid,²⁰² and for ChCl: citric acid, ChCl:lactic acid, ChCl:maltose, and ChCl: glycerol DESs during olive pomace extraction, attributed to sugar-mediated reduction.¹²⁸

Flavonoid-specific assays are also affected. Yatsyshina *et al.*²⁰³ demonstrated that AlCl₃-based total flavonoid determination suffers >98% signal suppression in acid-based DES due to carboxylate–Al³⁺ binding, with additional interference from ChCl (25%) and polyols, *i.e.*, ethylene glycol, 23.8% or sugars, *i.e.*, fructose, glucose, sorbitol: 21.5–19.2%, likely due to ionic and hydrogen-bonding interactions with Al³⁺ or the flavonoid chromophore.

Electrochemical techniques represent a robust alternative, offering rapid, low-cost, reagent-free, and pH-independent detection even in turbid DES matrices. These methods, based on cyclic voltammetry or differential pulse voltammetry, directly measure the collective redox activity of polyphenols²⁰⁴ and have been validated in complex matrices such as honey, and wine.²⁰⁵ For instance, Ismail *et al.* developed a sensitive electrochemical method for quercetin quantification in glucose-, fructose-, citric acid-, and lactic acid-based DESs using unmodified screen-printed electrodes. Percevault *et al.*,²⁰⁶ extended this approach to nine phenolics, demonstrating accurate quantification in betaine- and ChCl-based DESs and confirming that F–C precipitation (*e.g.*, in ChCl: ethylene glycol 1:2 and betaine:

citric acid 2:3) renders spectrophotometry unreliable. Other sophisticated approaches, such as measuring self-diffusion coefficients by NMR (*e.g.*, DOSY-NMR), enable the structural identification and mixture deconvolution in biomass structures, including lignin and monomeric aromatic phenol-derived molecules, providing molecular-level evidence of bioactive motifs.²⁰⁷

Examples of functional materials incorporating DES extracts, for use in pharmaceutical, cosmetic, agricultural, and food industries

As highlighted in the introduction, one of the most compelling advantages of DES-mediated phytochemical extraction lies in its compositional tunability. This adaptability not only enables efficient solubilization of diverse phytochemicals but also permits the rational design of application-ready DES-phytochemical systems that are safe, non-toxic, edible, and biodegradable—traits that support direct integration into functional materials.³⁸ Such DES-extract combinations are now being investigated across the pharmaceutical, agricultural, and food sectors (Fig. 6).

In pharmaceuticals, DES matrices enable novel liquid drug delivery systems in which encapsulated bioactive compounds benefit from controlled release, improved bioavailability, and enhanced physicochemical stability.²⁰⁸ In the agriculture and food industries, DES-extract composites have been applied as eco-friendly pesticides,⁷ fertilizers,²⁰⁹ and natural additives/preservatives,²¹⁰ offering nutritional enhancement and extended shelf life. Rich botanical extracts, combined with DES, can also yield food-grade colorants, flavors, and antioxidants with enhanced solubility and stability.^{211,212}

Overall, the incorporation of DES and extracts from agricultural waste and food by-products into functional materials showcases the potential for transforming underutilized resources into valuable solutions across diverse industries. This innovative approach aligns with the principles of sustainability and green chemistry, addressing challenges and meeting the demands of today's ever-evolving markets.⁷

Emulsions and creams

The pharmaceutical, cosmetic, personal care, veterinary, and food sectors increasingly demand formulations that are stable, user-friendly, rapidly absorbed, and capable of delivering targeted functionality. Emulsions, creams, and waxes remain preferred carriers for bioactive natural or inorganic compounds, as their biphasic architecture protects active ingredients from degradation while enabling controlled delivery.¹⁶⁷ Although transdermal drug delivery is often limited by low dermal permeability, the supramolecular organization of DESs can enhance solute diffusion within the stratum corneum and increase the solubility of active compounds, thereby improving their transdermal bioavailability.²⁸



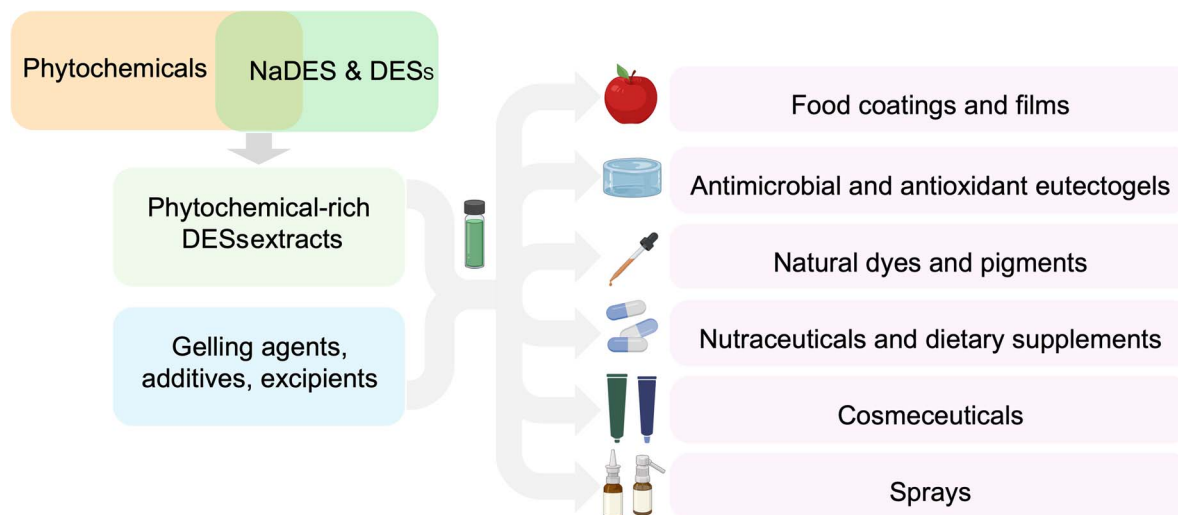


Fig. 6 DESs as multifunctional platforms for advanced materials, biomedicine, and sustainable processing applications. Figures created with BioRender®.

Despite their promise, the direct integration of DES-derived phytochemicals into cosmeceuticals remains underexplored. Regulatory considerations are critical: ChCl, widely used in DES preparation, is restricted in cosmetics by the European Union and FDA due to potential skin irritation, unpleasant odor, and its ability to enhance dermal penetration beyond the epidermis—an action permissible only for dermatological drugs.²⁵ Consequently, ChCl-based DESs are generally limited to research applications, whereas betaine-based DESs offer a safer and more permitted alternative for industrial use.

Recent advances illustrate the potential of DES-extract systems in cosmetics. Vasyliiev *et al.*²¹³ extracted flavonoids and phenolic acids from tomato pomace using ChCl:lactic acid and 1,2-propanediol DESs, incorporating the extracts into antioxidant and antibacterial emulsions. Pontes *et al.* (188) optimized phenolic recovery from olive pomace using ChCl:malonic acid, producing oil-in-water emulsions that retained their radical scavenging, antibacterial, and antifungal activities without further purification. Jamaledine *et al.*²¹⁴ developed diverse cosmetic formats—including peel-off masks, lip balms, facial masks, and moisturizers—each enriched with tomato pomace extracts obtained from NaDESs of tailored polarity. Rocha *et al.*²¹⁵ incorporated flavonoid-rich cork extracts into antioxidant and antibacterial creams using lactic acid-based DESs. Comparable work has leveraged DESs for topical formulations from *Ginkgo biloba*, *Cinnamomum camphora*, *Cryptomeria japonica*,²¹⁶ *Morus alba*,²¹⁷ *Spirulina*,²¹⁸ green tea,²¹⁹ Greek propolis,²²⁰ and *Calendula officinalis*.²²¹

Industrial adoption is emerging. For example, Gattefossé S.A.S. patented DES-based extraction of bioactives from *Calendula officinalis* and *Aesculus hippocastanum* for cosmetic emulsions, while Naturex patented betaine-based DES extraction from saffron, cherry blossoms, horsetail, and other botanicals for cosmetics, nutraceuticals, and pharmaceuticals.²⁵ These examples underscore the versatility of DES-phytochemical systems for next-generation dermal, nutritional, and therapeutic products.

Sprays

The integration of DESs into spray-based formulations offers notable advantages across the agriculture, cosmetics, pharmaceutical, and food industries, primarily by enhancing solubility, stability, and delivery efficiency while maintaining environmental sustainability.^{7,8} In agriculture, DES sprays can improve the uptake and persistence of pesticides and fertilizers, while in cosmetics and pharmaceuticals, they facilitate the solubilization and dermal or mucosal delivery of active compounds. Recent advances illustrate the breadth of applications. Arunachalam *et al.*²²² formulated trichome-mimicking adhesive sprays for pest control against western flower thrips using a D-glucose : D-fructose : sucrose : water 1 : 1 : 1 : 11 molar ratio containing 0.5–2 wt% hyaluronic acid. The mixture's viscosity and elasticity enabled the deposition as discrete microdroplets on plant leaves, enhancing adherence. In a distinct application, Jian *et al.*²²³ employed a betaine:glycerol 1 : 2 molar ratio NaDES to improve the survival of *Lactobacillus bulgaricus* sp1.1 during spray drying, achieving a 30.54% increase in viability—underscoring potential uses in functional foods and nutraceuticals.

DESs are also emerging as stabilizing agents in encapsulation technologies designed to protect labile bioactives. Basar *et al.*²²⁴ encapsulated β-carotene in whey protein concentrate *via* emulsion electro-spraying, incorporating a 10% ChCl : butanediol 1 : 2 molar ratio DES. This formulation preserved the stability of β-carotene for 180 min, whereas the free compound degraded completely over the same period. These studies collectively highlight DES-based sprays and encapsulation systems as versatile, eco-compatible platforms for enhancing performance and stability in diverse industrial sectors.

Eutectogels as edible films and food coatings

The development of biodegradable, edible films and coatings for food contact applications has intensified in recent years, driven by the need for non-toxic, environmentally compatible materials capable of extending shelf life. Functionality can be



enhanced through the incorporation of antioxidant and antibacterial agents extracted from biomass.²²⁵

When polymers or gelling agents are incorporated into DESs, extensive hydrogen-bonding networks and non-covalent, transient interactions are formed. These supramolecular assemblies give rise to eutectogels—three-dimensional polymeric or colloidal networks in which the DES is immobilized. Eutectogels combine the environmental stability of organogels with the hydration capacity of hydrogels, while exhibiting enhanced mechanical strength, stretchability, self-healing, and anti-freezing properties.²²⁶

Their transient, reversible interactions impart intrinsic biodegradability, and when composed of food- or pharmaceutical-grade components, low toxicity and broad biocompatibility. In addition, eutectogels can be obtained either *via* direct gelation—using biopolymers (*e.g.*, gelatin, gums), linear polymers (*e.g.*, PEG, PVA), or low-molecular-weight gelators (LMWGs)—or *via in situ* polymerization of monomers (*e.g.*, acrylic acid, methacrylic acid, itaconic acid) within the DES phase (typically used as HBD), producing crosslinked polyacrylates whose mechanical properties and release kinetics are tunable through crosslink density and interaction strength.^{15,227}

Beyond polymer-based designs, phytochemicals can act as structuring agents, forming eutectogels through hydrogen bonding and other supramolecular interactions, thereby imparting additional mechanical, physicochemical, and bioactive properties.²²⁸

Several studies highlight the versatility of this approach. For instance, Chandra Roy *et al.*¹⁵² extracted astaxanthin (>65 $\mu\text{g g}^{-1}$ yield) from shrimp waste using ChCl : lactic acid 1 : 1.02 molar ratio, then prepared a chitosan-based edible coating. The DES acidity facilitated the dissolution of chitosan, and the astaxanthin conferred potent antioxidant activity. Kyriakidou *et al.*,²²⁹ used ChCl : glycerol 1 : 11 molar ratio to extract 20.12 mg QE g^{-1} flavonoids from pomegranate peel; incorporation into chitosan films increased moisture absorption and improved thermal and physicochemical stability. On the other hand, Mostafa *et al.*,²³⁰ employed ChCl : glycerol 2 : 1 molar ratio to extract phenolic acids from date palm leaves and incorporated them into soybean protein isolate films, enhancing antioxidant and antibacterial properties alongside mechanical performance.

Colorimetric active packaging has also been developed. Thakur *et al.*,²³¹ extracted anthocyanins from black rice using a lactic acid:fructose 5 : 1 molar ratio, producing PVA-based edible films that acted as natural pH indicators *via* reversible color change, supported by thermal, mechanical, and physicochemical analyses. Velásquez *et al.*,²³² similarly prepared κ -carrageenan films containing anthocyanin-rich extracts of *L. chequen* fruits obtained with lactic acid:glucose 8 : 1 molar ratio, yielding materials with both antioxidant and antibacterial activities. Collectively, these works demonstrate that eutectogel- and DES-based edible films and coatings can serve as multifunctional materials for sustainable food preservation, combining active protection, environmental compatibility, and tunable physicochemical properties.

Natural dyes

The industrialized food sector increasingly demands natural-ingredient products that not only meet nutritional and sensory expectations but also deliver added health benefits. Natural pigments are particularly attractive as they impart vivid coloration while often providing antioxidant activity, depending on their botanical origin and the presence of bioactive moieties. DESs have emerged as promising solvents for the extraction and stabilization of natural pigments. For example, Dai *et al.*²³³ demonstrated that carthamin, a thermolabile red pigment from safflower (*Carthamus tinctorius* L.), exhibited fivefold greater stability at 40 °C in xylitol : ChCl DES compared with its stability at 60 °C, and eightfold greater stability than in water at the same temperature. Similarly, Jelinski *et al.*²³⁴ showed that curcumin dissolved in ChCl:glycerol remained fully stable under 120 min of artificial sunlight exposure, whereas methanolic curcumin degraded to 5% of its initial concentration. In an applied example, Jorge *et al.*²³⁵ employed glycerol : urea 1 : 1 molar ratio and 20 wt% water to solubilize curcumin for cotton dyeing, integrating the process into a circular economy framework.

Among natural colorants, anthocyanins are the most widely studied due to their safety, intense color, pH-dependent chromaticity, and bioactivity. Numerous DES-based extraction studies target agricultural by-products, including blueberry leaves and pomace, mulberry, strawberry, bilberry, raspberry, cranberry, blackberry, chokeberry, sour cherry peels and pomace, grape pomace, saffron waste, black rice bran, *Hibiscus sabdariffa* calyces, black carrots, black bean hulls, and rose petals, among others.²³⁶ For instance, Jeong *et al.*²³⁷ reported that ChCl : citric acid : D-(+)-maltose significantly outperformed 80% aqueous MeOH for grape skin anthocyanin recovery.

On the other hand, carotenoids—yellow, orange, or red tetraterpenoids—have also been efficiently extracted using hydrophobic DES from pumpkin peel,¹⁴⁹ orange peel,²³⁸ *Spirulina platensis*,²³⁹ *Nannochloropsis oculata*,²⁴⁰ kale waste,²⁴¹ persimmon by-products,²⁴² tomato pomace,²⁴³ and *Mauritia flexuosa* fruit.²⁴⁴ In the same line, betalains, nitrogen-containing pigments with antioxidant capacity, have been extracted from beetroot waste²⁴⁵ and dragon fruit peel²⁴⁶ with high yields.

Concentrated and dispersible nutraceuticals

There is a growing demand for innovation in plant-derived pharmaceuticals, nutraceuticals, and dietary supplements, driven by both the need for environmentally sustainable extraction technologies and the limited oral bioavailability of many bioactive phytochemicals. Several *in vitro* studies have demonstrated that phenolic-rich grape skin extracts obtained using DESs exhibit high antioxidant activity and low cytotoxicity, supporting their potential as ready-to-use extracts for therapeutic and nutritional applications.^{120,129,208,247}

In a targeted *in vivo* study, da Silva *et al.*²⁴⁸ assessed the gastroprotective effects of a crude blueberry extract obtained using ChCl : glycerol : citric acid 0.5 : 2 : 0.5 molar ratio. The following fractionation into an anthocyanin-rich fraction and a non-anthocyanin phenolic fraction was administered to rats over 14 days before ethanol-induced gastric ulceration. The



DES-based crude extract mitigated oxidative stress and neutrophil infiltration, demonstrating gastroprotective effects and suggesting its potential as a nutritional adjuvant for ulcer prevention.

Similarly, Dal Bosco *et al.*²⁴⁹ reported the development of a *l*-menthol:butylated hydroxytoluene 3:1 molar ratio with intrinsic antioxidant properties. Designed for the liquid–liquid extraction of lipophilic micronutrients from aqueous matrices, such as fruit juices, the system effectively extracts and preserves β -carotene and α -tocopherol acetate, providing both enhanced stability and immediate applicability without the need for further purification.

Conclusions

The application of DESs, and eutectic systems more broadly, has emerged as a green and sustainable strategy for extracting phytochemicals and other nutraceuticals from agri-food residues and processing by-products. Compared with other alternative solvents such as ionic liquids, DESs offer several key advantages, including low cost, straightforward preparation, reusability, high extraction efficiency, and—when appropriately formulated—biocompatibility and biodegradability. As customizable designer solvents, DESs can be tailored to selectively target and recover specific classes of bioactive compounds for applications in the food, pharmaceutical, and allied sectors. Their tunable nature also facilitates integration with other green extraction technologies, including ultrasound-assisted, microwave-assisted, and enzymatic extraction, enabling the efficient recovery of diverse types of secondary metabolites.

Beyond extraction, DES-derived bioactive fractions from food by-products can be repurposed for primary production, such as biopesticides or biofertilizers, thereby closing nutrient loops and contributing to a circular economy. Such extracts may also be directly incorporated into the food chain as natural preservatives or active coatings, extending the shelf life and quality of fresh produce.

Ongoing research is required to comprehensively evaluate DES toxicity, life-cycle impacts, and interactions with biological systems, which can be strongly influenced by concentration, water content, and degree of dilution. Critical knowledge gaps include *in vivo* bioavailability and bio-accessibility of DES-dissolved phytochemicals, as well as the potential for eutrophication following their release into aquatic environments. Importantly, the inherently low volatility of DESs allows for their direct use as “ready-to-use” extracts without the need for solvent removal. Their formulation from GRAS- or FDA-approved HBAs and HBDs enables their function as excipients, carriers, or solubilization media with enhanced stability and, in some cases, intrinsic bioactivity.

Although spectrophotometric assays remain popular in phytochemical analysis due to their simplicity and low cost, the potential for molecular interferences from DES matrices can lead to overestimation of target analytes. This has led to an increased adoption of chromatographic and electrochemical methods in DES-based extraction workflows. Further investigation is warranted to determine whether similar matrix effects

compromise other colorimetric assays, including those for flavonoid, carotenoid quantification, and antioxidant capacity (*e.g.*, DPPH, ABTS, FRAP, ORAC).

Looking forward, the development of DES-based functional materials—including eutectogels, nutraceutical systems, nanocomposites, natural pigments, emulsions, and cosmeceuticals—offers opportunities to enhance process efficiency, reduce costs, and improve the mechanical, thermal, and physicochemical performance of final products. These advances arise from the synergistic combination of phytochemical-derived bioactivities with the tailored physicochemical interactions afforded by DES components, aligning with the core principles of green chemistry to support sustainability in emerging bio-based industries, particularly those serving food, nutrition, and health markets.

Author contributions

Luis Alfonso Jiménez-Ortega: writing—original draft, methodology/investigation, conceptualization, visualization. Marta Marques: writing—original draft. María Priscila Quiñonez-Angulo: writing—original draft. Alexandre Paiva: review and editing. Ana Rita C. Duarte: conceptualization, visualization, review, and editing. José Basilio Heredia: visualization, review, and editing. Josué D. Mota-Morales: conceptualization, visualization, review, and editing.

Conflicts of interest

The authors declare no competing interests.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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