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From batch to flow: integrating in-line (deep) eutectic solvents with sequential downstream processing for sustainable biomass valorization

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(Deep) eutectic solvents (DES) have emerged as versatile and tunable alternatives to conventional solvents for biomass valorization. Nevertheless, most DES-based processes are still performed in static (batch) configurations, which limit scalability, reduce processing efficiency, and increase both cycle downtime and the number of operational steps. These limitations can be significantly mitigated in semi-continuous or continuous-flow systems, where intensified mass and energy transfer, together with improved control over kinetic and thermodynamic parameters, enable more efficient operations. This review critically advocates a transition in DES-based extraction systems toward process intensification, aligned with the principles of green chemistry and green engineering. Particular emphasis is placed on the transition from batch to (semi)continuous modes integrated with sequential downstream steps and real-time analysis, for which several potential process configurations are proposed. Hybrid systems combining pressurized-DES extraction with solid-phase extraction (SPE), membrane separation, or liquid–liquid extraction (LLE) are discussed for their potential to enhance concentration, fractionation, and purification of valuable compounds derived from biomass. Finally, this review outlines future directions, including the integration of sustainability metrics and the adoption of artificial intelligence (AI)-assisted solvent selection and process optimization, paving the way for next-generation DES-based (semi)continuous biorefineries.

Green foundation

1. Our work advances green chemistry by shifting DES-based biomass extraction from static batch experiments toward intensified (semi)continuous-flow and integrated downstream processing, improving scalability, selectivity, and alignment with green chemistry and green engineering principles.
2. Our main achievement is a critical demonstration that sustainability is not intrinsic to DES chemistry alone, but strongly depends on process configuration, solvent recovery, and energy demand. We highlight hybrid flow platforms coupling DES extraction with SPE, membranes, or LLE, enabling sequential fractionation, reduced solvent use, and real-time analytical control.
3. Further greening requires pilot-scale validation, standardized sustainability metrics (energy intensity, recyclability, life cycle assessment), improved solvent recovery loops, DES-compatible equipment, and AI-assisted solvent/process optimization supported by high-quality experimental datasets.

Introduction

Among the alternative solvents explored for biomass valorization, (deep) eutectic solvents (DES) have emerged as one of the most widely used classes. Their tunable physicochemical properties and broad applicability enable the extraction of valuable compounds from a diverse range of natural matrices, from small bioactive molecules to structurally complex constituents.[1,2] However, DES have predominantly been applied in biomass valorization through batch extraction processes. In the batch configuration, the solvent and solid matrix are combined in a closed vessel, and extraction occurs without solvent renewal, although mechanical agitation, ultrasound, or microwave irradiation may be applied to enhance mass and energy transfer.[3,4] Even with such improvements, batch processes remain constrained by the absence of continuous solvent flow. Consequently, they exhibit reduced mass-transfer

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rates and limited scalability when compared to continuous-flow operations.[5–7] While DES are frequently described as green or sustainable alternatives to conventional organic solvents, it is important to emphasize that they should be regarded as potentially greener rather than inherently green. Their overall sustainability is highly process-dependent and critically influenced by solvent recovery efficiency (typically >95%), the number of reuse cycles, and the energy intensity associated with solvent handling, heating, and pressurization.

A transition toward (semi)continuous operations not only alleviates kinetics and operational limitations but also opens new opportunities for integrating downstream separation steps directly in-line with the extraction. In such systems, the extract can be fed continuously into fractionation or purification modules, including solid-phase extraction (SPE), membrane units, or liquid–liquid fractionation systems.[8–11] This configuration further allow the incorporation of real-time analytical strategies, for example, coupling the extraction unit with an on-line HPLC-PDA system, which improves process control and supports continuous, data-driven decision-making under near steady-state conditions.[12] Continuous integration also reduces manual handling and material use, limits exposure to air and light, minimizes degradation of sensitive molecules, and facilitates steady-state operations. As a result, reproducibility improves and real-time monitoring and control are facilitated.[13]

Moreover, DES-based (semi)continuous systems align closely with principles of green chemistry and green engineering.[14–17] Fig. 1 presents a design-oriented framework that maps the key operational features of DES-based (semi)continuous extraction to the relevant green chemistry (https://www.acs.org/green-chemistry-sustainability/principles/12-principles-of-green-chemistry.html) and green engineering principles (https://www.acs.org/green-chemistry-sustainability/principles/12-design-principles-of-green-engineering.html). This framework guides the selection and configuration of the

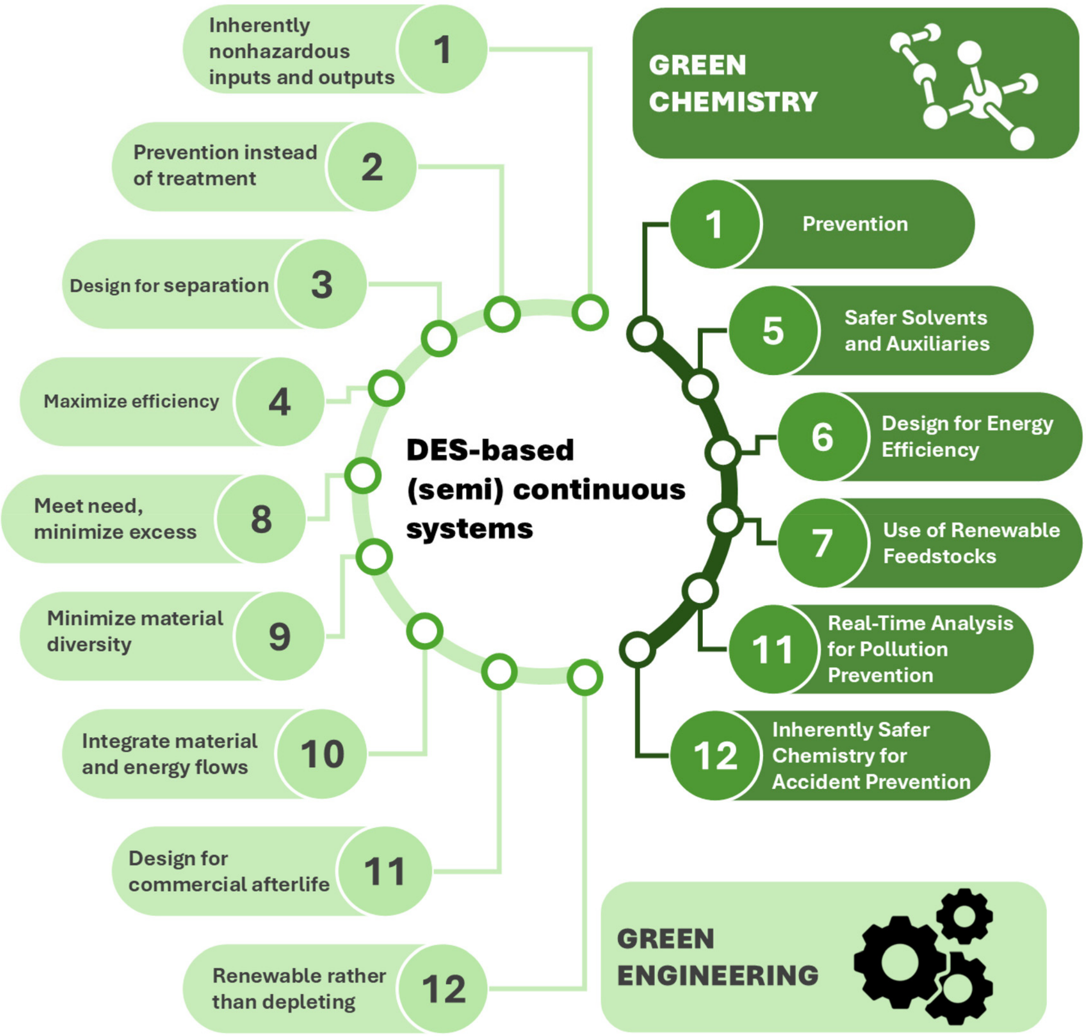

Fig. 1 Key principles of green chemistry and green engineering aligned with DES-based (semi)continuous extraction systems for biomass valorisation. Original figure created by the authors. Icons were used as graphical elements under a Flaticon premium license (no attribution required).

process modules. Beyond functioning as a classification scheme, Fig. 1 links each principle to a specific physical attribute of the extraction platform, allowing researchers to determine which design choices support compliance with defined sustainability criteria.

Principles related to solvent selection address the basic properties of the DES phase. When the selected DES is composed of renewable, non-toxic constituents, as usually found in NADES-based on sugars, amino acids, or organic acids, the system could fulfils green chemistry principles 1 (prevention), 5 (safer solvents and auxiliaries), 7 (use of renewable feedstocks), and 12 (inherently safer chemistry for accident prevention), as well as green engineering principle 1 (inherently nonhazardous inputs and outputs) and 12 (renewable rather than depleting).[18,19] In practice, these principles translate into measurable solvent-related descriptors that can be evaluated using environmental, health, and safety (EHS) profiles. In this context, the adoption of sustainable energy sources to power the extraction process could further strengthen alignment with these principles, particularly regarding energy-related environmental impacts.

A second group of principles is related with process configuration and intensification. The reduction and integration of processing steps, such as the coupling purification or fractionation modules, may also contribute to green engineering principle 2 (prevention instead of treatment) and principle 3 (design for separation). Similarly, enhanced mass-transfer efficiency, achieved by designed systems for reducing DES viscosity and increasing diffusivity within the biomass matrix, aligns with green engineering principle 4 (maximize efficiency) and green chemistry principle 6 (design for energy efficiency). These improvements are quantified using process metrics such as solvent-to-feed ratio, extraction yield per unit time (throughput), and energy consumption per kilogram of product. A detailed evaluation of these metrics is provided in the section Advantages of in-line systems: a comparative analysis. However, the extent to which these features provide environmental benefits should be quantified individually, using methods such as life cycle assessments (LCA).[20,21] For example, Zaib *et al.* (2022) demonstrated by a cradle-to-gate LCA that the environmental performance of DES is not inherently superior.[22] For instance, choline chloride (ChCl) : urea (1 : 2, molar ratio) exhibited lower environmental impacts than dichloromethane and ethyl acetate, but higher impacts than methanol and ethanol. Notably, ChCl : citric acid (1 : 1, molar ratio) showed the highest environmental impacts among the evaluated ChCl-based DESs.

A third group of principles addresses real-time process monitoring. Integrating real-time analytical tools, whether online or in-line, is a valuable yet underexplored strategy.[12] This approach enables (semi)continuous systems to follow the guidance of green chemistry principle 11 (real-time analysis for pollution prevention) and to establish more robust criteria for process continuation, interruption, and quality control. These tools provide real-time feedback on extraction or reaction kinetics, target analyte concentrations, co-extraction events, undesirable side reactions, and breakthrough behaviour.

A fourth group of strategies focuses on resource efficiency and material circularity. Green engineering principle 8 (meet need, minimize excess) could be achieved when the (semi)continuous flow regime delivers only the solvent volume necessary to reach the target yield, rather than relying on fixed solvent-to-feed ratios as in conventional batch configurations. Moreover, employing a single DES or a minimal set of structurally related solvents throughout sequential extraction, reaction, or purification stages supports green engineering principle 9 (minimize material diversity). Additionally, green engineering principle 10 (integrate material and energy flows) is addressed by configurations in which, for instance, the heat supplied for reactions or pressurised extraction is also used for downstream DES-assisted fractionation. In the same manner, the spent DES phase can be recovered and recirculated *via* in-line collection modules, thereby closing the material loop within a single operational sequence.

Lastly, green engineering principle 11 (design for commercial afterlife) is addressed at two levels. First, the modular architecture of (semi)continuous platforms enables adaptation, disassembly, and reconfiguration for various biomass feedstocks and target compounds, thereby extending equipment utility beyond a single application. Second, DES-derived products and co-products, such as biochar from *in situ* carbonisation and recovered solvent phases, may be redirected to secondary applications,[23] including adsorption materials or solvent-reuse cycles.[24] This approach ensures that both process infrastructure and the resulting material streams retain value beyond the primary valorization objective.

To the best of our knowledge, this perspective provides the first comprehensive overview of DES-based extraction processes for biomass valorisation integrating in-line downstream purification and fractionation steps, as well as the potential incorporation of real-time analytical tools. While DES have been extensively reviewed from a fundamental perspective and for their practical use in the extraction of natural products, no previous work has shown how pressurized DES-assisted extraction can be operationally integrated with downstream unit operations such as SPE, membrane separations, or other modular strategies. Therefore, this review fills a critical gap in the literature by providing the first comprehensive perspective on DES-based systems moving beyond batch operations toward modular, (semi)continuous, and more sustainable processing approaches. This integrated viewpoint aligns with the principles of green chemistry and green engineering by combining the advantages of DES and (semi)continuous approaches. Finally, it unlocks new, and more sustainable pathways for biomass valorisation.

The role of the solvent in biomass valorisation

Conceptual aspects on solvent selection

Solvents form the central connection between the extraction, fractionation, and purification of valuable compounds from biomass and their subsequent transformation into useful products and materials.[25] Biomass can have its origin in a wide range of sources, including food and agroforest wastes, algae, plants, fungi, bacteria among others, and may contain compounds with diverse applications. These range from alkaloids for pharmaceutical use to phenolic compounds for food applications, as well as chemical platforms for industrial processes (Fig. 2). In most cases, however, recovering such valuable compounds requires solvent-based procedures; only in limited circumstances can mechanical pressing alone extract a valuable fraction (*e.g.* oils or juices).

A systematic approach to solvent selection can be supported by the CHEM21 solvent selection guide, which offers a structured framework for ranking solvents according to their EHS profiles.[26] By categorizing solvents as recommended, problematic, or hazardous, the guide assists researchers in identifying greener alternatives to conventional options. Nevertheless, solvent selection also depends on broader factors, including energy consumption, waste generation, and circularity considerations such as recycling and reuse.[27,28] As highlighted in the critical review prepared by Hessel *et al.* (2022), the solvent sustainability should therefore be assessed using holistic tools that integrate green chemistry principles, LCA, and circular-economy metrics, including the 10R framework.[27] Such an integrative approach enables solvent choices that balance process efficiency with environmental and social impacts. For DES, EHS factors should be addressed at both the component and system levels, as final mixtures may display toxicity and environmental profiles distinct from those of their individual constituents. Accordingly, constituent-based screening should be complemented by system-level evaluation, including toxicity and biodegradability assays, while Quantitative Structure Toxicity Relationships (QSTR)-based approaches may provide useful support for preliminary hazard screening and the rational design of potentially safer DES.[29,30]

On the other hand, the solvent employed in the extraction, especially when followed by fractionation or purification, must also be efficient, selective, and compatible with subsequent downstream operations. Solvent performance is governed by properties such as hydrophobicity/hydrophilicity, acidity/basicity, and the ability to form miscibility gaps with other solvents, as well as by the interplay between kinetic and thermo-

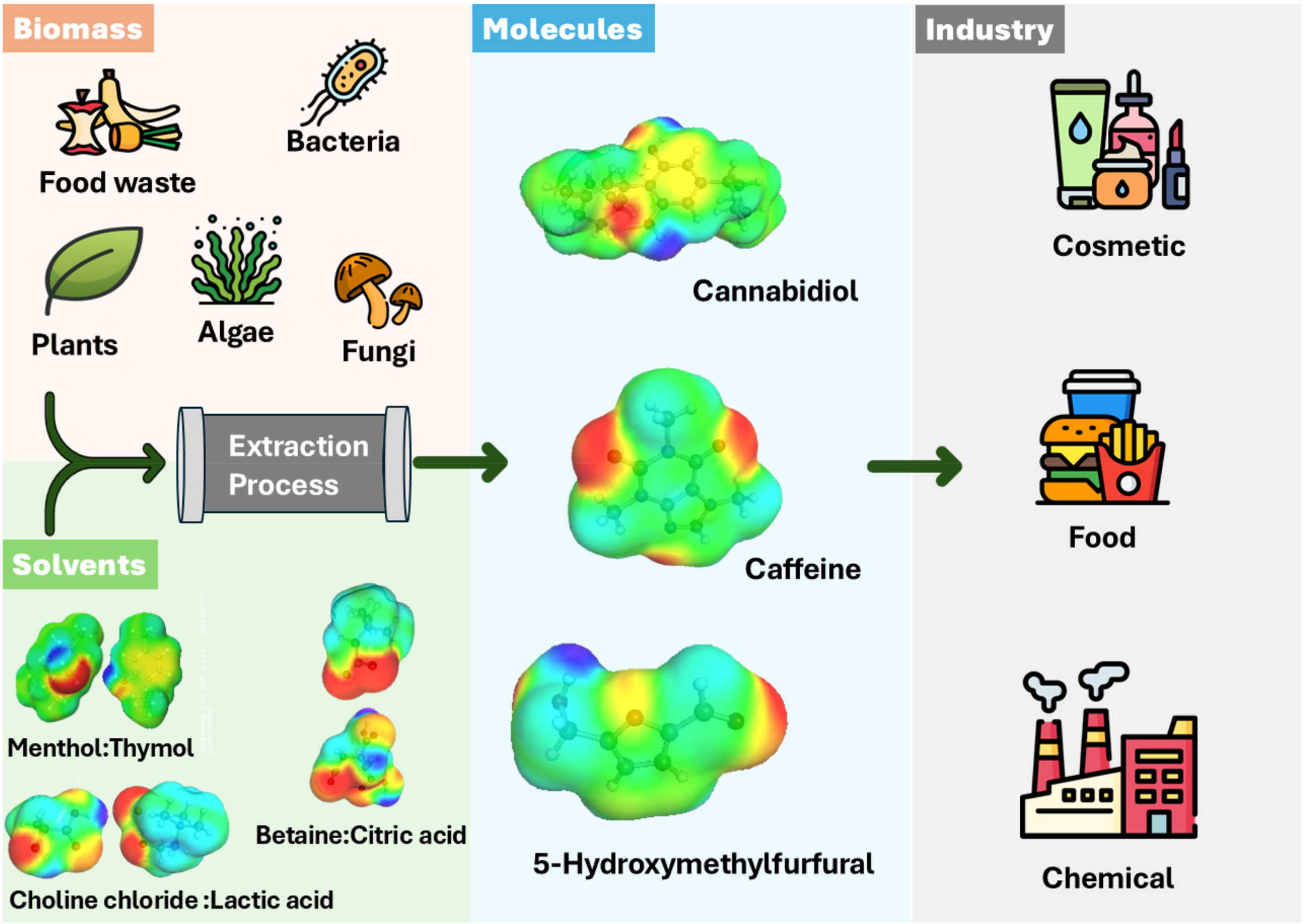

Fig. 2 Schematic representation of solvent-based extraction of valuable biomass-derived compounds and their subsequent applications in the cosmetic, food, and chemical industries. Original figure created by the authors. Icons were used as graphical elements under a Flaticon premium license (no attribution required).

dynamic factors that determine their extraction behaviour.[31,32] From a kinetic perspective, an ideal solvent facilitates mass transfer of target molecules from the solid matrix into the liquid phase.[33] Parameters such as viscosity, diffusivity, and solvent penetration capacity directly affect the rate at which solutes migrate through the biomass. High viscosity, common in many DES, hinders mass transfer and slows extraction. Fyfe *et al.* (2025) showed that such feature leads to prolonged mixing times and persistent concentration gradients.[34] Nevertheless, increasing temperature or applying pressure can enhance mass transfer and improve solvent penetration. From a thermodynamic perspective, solute–solvent interactions, including the chemical potentials of the individual components and associated enthalpic, entropic, and Gibbs free energy contributions, govern the extent of solute dissolution.[35,36] Favorable solute-solvent compatibility enhances the partitioning of the target compounds into the solvent phase, thereby improving the extraction efficiency parameters.

In this context, computational tools such as Hansen Solubility Parameters and the Conductor-like Screening Model for Real Solvents (COSMO-RS) have emerged as valuable approaches for solvent screening.[37] The Hansen Solubility Parameters estimates solubility based on three fundamental interaction forces, dispersion, polarity, and hydrogen bonding, placing solvents and solutes in a three-dimensional space, where closer proximity indicates greater compatibility.[38] COSMO-RS, by contrast, employs quantum-calculated surface charge densities to predict thermodynamic properties such as solubility, activity coefficients, and partitioning behaviour.[39,40] By evaluating the chemical potential of solvents and solute species, COSMO-RS provides insights into solvation phenomena and enables high-throughput screening of large solvent libraries, including DES formulations. For instance, Contieri *et al.* (2023) used COSMO-RS thermodynamic modeling to screen 10 585 potential DES combinations.[41] In their study, the solvation capacity was evaluated for two phenolic markers, artepillin C and *p*-coumaric acid. The screening identified several promising betaine-based mixtures, most notably betaine : citric acid (1 : 2, molar ratio), as highly effective candidates for extracting polyphenols from Brazilian green propolis.

DES and other alternatives

Among the promising solvents employed in biomass valorization, DES have emerged as an outstanding alternative. Compared to conventional volatile organic compounds (VOCs), if well selected, they offer several advantages, including negligible vapor pressure, low flammability, and high thermal stability.[42] From a thermodynamic perspective, DES constitute a particular subclass of eutectic mixtures whose definition relies on non-ideal liquid behaviour.[43] A DES is formed only when the liquid phase shows enthalpy-driven negative deviations from ideality, resulting in a eutectic temperature markedly lower than that predicted for an ideal mixture. This behavior arises when the interactions between the components, typically a Lewis or Brønsted acid-base pair, are stronger than the self-interactions present in the pure compounds. Such enhanced interactions allow a solid precursor to become liquid at the operating temperature while remaining compositionally tunable beyond the exact eutectic ratio.[42] Importantly, the mere presence of hydrogen bonding or a simple melting-point depression is insufficient to classify a mixture as a DES, as most binary solids form eutectics without displaying negative non-ideality.[44] Only systems that show substantial negative deviations from ideal liquid behavior legitimately deserve the descriptor “deep”. DES have been classified into five types based on the nature of their constituents (Fig. 3).[42,45] Types I–IV are ionic and comprise combinations of quaternary ammonium or phosphonium salts (QAS/QPS) with metal salts (Type I, *e.g.* ChCl + $ZnCl_2$), hydrated metal salts (Type II, *e.g.* ChCl + $CoCl_2·6H_2O$), hydrogen bond donors (Type III, *e.g.* ChCl + urea), or metal salts combined with HBDs in the absence of a quaternary salt (Type IV, *e.g.* $ZnCl_2$ + urea). Type V DES, introduced by Abranches *et al.* (2019), are composed entirely of non-ionic molecular substances.[46] A representative example is the thymol–menthol system, where the phenolic proton of thymol forms a hydrogen bond with the aliphatic oxygen of menthol that is significantly stronger (−14.8 kJ mol^{-1}) than those present in either pure liquid.[46]

One additional advantage of some DES is that they can be derived from renewable, biodegradable components, thereby greatly reducing their environmental and safety risks.[47] In this case, a particularly relevant subgroup is the Natural Deep Eutectic Solvents (NADES). NADES are eutectic mixtures whose components are natural metabolites found in organisms, encompassing quaternary ammonium compounds, organic acids, amino acids, sugars, and fatty acids.[18] Since their initial proposition, based on the hypothesis that they serve fundamental biological roles such as cryoprotection and metabolite stabilization within cells, NADES have been extensively utilized in green technologies, most notably for the extraction of bioactive compounds.[18] Thermodynamically verified examples include betaine–urea and betaine–thymol mixtures, where the zwitterionic character of betaine, which is an excellent HBA, promotes strong negative deviations from ideality with a wide range of HBDs, effectively making betaine a universal DES-forming compound.[48]

However, DES and NADES nomenclature have often been decoupled from the fundamental knowledge regarding their phase equilibria and molecular interactions. To address common ambiguities and the emphasis on practical performance over strict thermodynamic compliance in many valorization fields, particularly as extraction media, a new conceptual framework has been proposed.

The term Mixtures based on Natural Compounds (MINACs) has been introduced to more accurately categorize mixtures composed of natural constituents whose “deep eutectic” nature is either unverified or intentionally compromised to achieve practical benefits.[49] For extraction and process-development applications, factors such as viscosity, cost, toxicity, biodegradability, and overall process compatibility may outweigh strict adherence to thermodynamic definitions. A

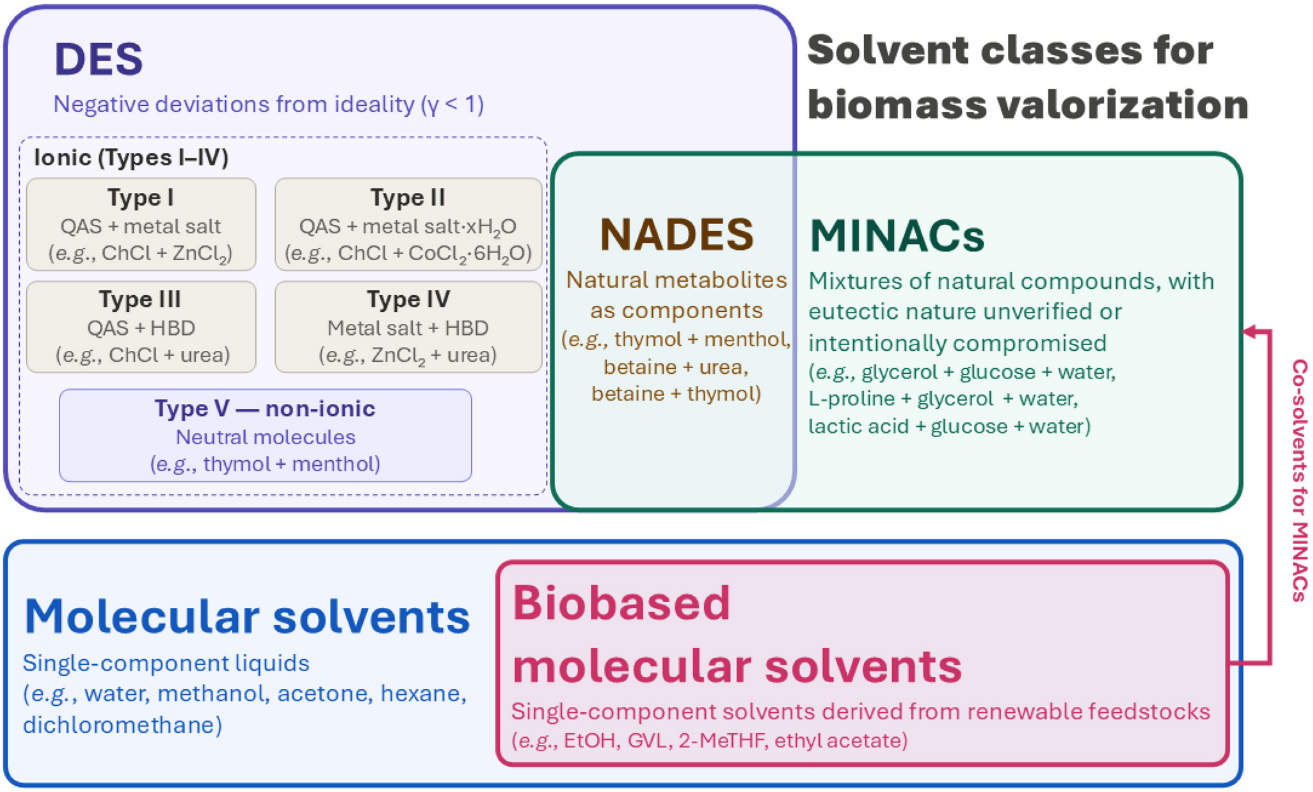

Fig. 3 Classification of solvent systems employed in biomass valorization. Deep eutectic solvents (DES) are defined by negative deviations from thermodynamic ideality ($\gamma < 1$) and are classified into five types (I–V) according to the nature of their components. Natural deep eutectic solvents (NADES) represent the subset of DES composed exclusively of natural metabolites with verified eutectic behavior. Mixtures based on natural compounds (MINACs) encompass a broader category that includes systems whose deep eutectic nature is either unverified or intentionally compromised through water addition or off-eutectic ratios. Biobased molecular solvents constitute a subclass of molecular solvents derived from renewable feedstocks and may also serve as co-solvents in MINACs formulations (dashed arrow). Other solvent classes relevant to biomass valorization but not depicted in this figure include ionic liquids (ILs), supercritical fluids (*e.g.*, $scCO_2$), and gas-expanded liquids (GXLs). Abbreviations: QAS, quaternary ammonium salt; HBD, hydrogen bond donor; ChCl, choline chloride; EtOH, ethanol; GVL, γ-valerolactone; 2-MeTHF, 2-methyltetrahydrofuran. Original figure created by the authors.

common strategy in application-focused studies is the intentional addition of water to reduce the inherently high viscosity of NADES and modulate their polarity, thereby creating a tunable extraction media.[50] However, the introduction of water, even at relatively low concentrations, can disrupt the (deep) eutectic structure, leading to component dissociation and effectively converting the system into an aqueous solution of natural compounds.[44] The MINACs definition addresses this practical limitation by encompassing systems including high levels of water or other molecular solvents that may not meet the strict criteria for classification as "deep eutectic". As such, MINACs offer a scientifically rigorous yet application-driven terminology for the development of sustainable solvent systems. This conceptual shift enables research to prioritise process performance and real-world applicability, supporting the development of ready-to-use extracts and sustainable formulations for the food and cosmetic sectors.[51,52] In this context, Yagmur *et al.* (2025) applied the MINACs framework in a case study involving Spirulina (*Arthrospira platensis*), targeting the valorization of its non-polar fraction rich in free fatty acids and pigments.[53] Using COSMO-RS calculations to rationally design MINACs, they screened a shortlist of 14 natural solvents and identified four caprylic acid-based eutectic systems as promising MINACs. These systems were subsequently validated experimentally for the recovery of fatty acids and pigments from Spirulina, demonstrating both the predictive power of the *in silico* approach and the potential of MINACs as tunable, sustainable solvents for cosmetic ingredient development.

Furthermore, the enhanced flexibility of MINACs may provide benefits for continuous flow applications, in contrast to the more restrictive behavior of strict DES systems. A recent rheological study indicates that several ChCl-based DES display non-Newtonian flow behavior, with sustained increases in viscosity under shear stress resulting from molecular compaction and partial water loss from the eutectic structure.[54] In some cases, the viscosity increased up to fourteen-fold relative to the initial value, and this thickening effect persisted over months, suggesting irreversible structural rearrangements, a phenomenon the authors termed *mnemopektic* behavior. In practice, prolonged exposure to shear stress in pumps, tubing, and mixing zones may progressively alter the rheological properties of the DES stream, potentially leading to increased backpressure, reduced flow uniformity, and compromised process stability.

Moreover, bio-based solvents, mainly those already produced from renewable materials such as ethanol, ethyl acetate, γ-valerolactone (GVL), 2-methyltetrahydrofuran (2-MeTHF), propylene carbonate, glycerol, and dimethyl carbonate, have emerged as promising green alternatives to petroleum-derived VOCs.[27,55] As discussed by Clavilier *et al.* (2025), many of these solvents can be obtained from biomass or carbon dioxide (CO_2)-based feedstocks, combining low toxicity, high biodegradability, and favorable safety profiles.[55] Their tunable polarity and miscibility make them suitable for extraction, liquid–liquid separation, and other key steps in biomass valorization. Within the context of MINACs, biobased molecular solvents may function as co-solvents to adjust the physicochemical properties of natural compound mixtures, thereby broadening the range of options for sustainable extraction media (Fig. 3).

Similarly, carbon dioxide, particularly in its supercritical state ($scCO_2$), is considered a more environmentally friendly alternative to conventional solvents. The combination of $scCO_2$ with DES-based systems offers a promising approach for sustainable processing, as discussed in the following section.[56,57] Fig. 3 presents the classification and interrelationships of the solvent systems discussed in this section, emphasizing the conceptual distinctions among DES, NADES, MINACs, and bio-based molecular solvents within the context of biomass valorization.

From batch to flow

One module

The first step toward shifting extraction from batch to flow can be achieved by implementing a semi-continuous operating mode.[7] In this scenario, the solid sample is maintained under static conditions while the solvent is continuously passed through the biomass within the extraction cell, enabling solvent renewal without disturbing the solid matrix.

Three principal approaches within this framework are discussed hereafter: (i) pressurized liquid extraction (PLE), in which DES are pumped under elevated pressure to enhance mass transfer and solvent penetration into the solid matrix. Unlike conventional molecular solvents, maintaining the liquid state is not a primary concern for DES due to their inherently high boiling points; (ii) supercritical fluid extraction (SFE), in which $scCO_2$ serves as the primary solvent, with DES functioning as a modifier to extend the polarity range; and (iii) gas-expanded liquid extraction (GXL), where the dissolution of pressurized CO_2 into the DES phase reduces viscosity and enhances diffusivity, as well as potentially enabling a switchable system. Each configuration imposes distinct physical property profiles, particularly regarding viscosity, phase behavior, and mass-transfer characteristics, that directly influence the selection and design of downstream separation modules, as discussed in the "Coupling Modules" section. It is important to mention, however, that all three techniques can also be operated in batch (or static) mode. Such configurations are not desirable when the objective is to advance toward semi-continuous operation, as static steps interrupt solvent renewal, reduce mass-transfer efficiency, and hinder integration with downstream processing units. A comprehensive overview of applications combining these techniques with green solvents has been reported by dos Santos *et al.* (2025).[58] As its name suggests, PLE uses liquid solvents under elevated pressure for the extraction process, without reaching supercritical conditions.[59,60] In PLE, analyte transport depends on the polarity and physicochemical properties of the solvent, which can be finely tuned through the combined application of pressure and temperature. Elevated temperatures increase analyte solubility, disrupt matrix–analyte interactions, and enhance diffusion rates, while high pressures ensure that the solvent remains in the liquid state.[60] Under these conditions, solvent viscosity and system surface tension are reduced, facilitating penetration into solid samples, improved recovery of compounds retained within matrix pores, and a simultaneous reduction in solvent consumption.[61]

Although the existence of a critical region was first reported by Cagniard de La Tour in the early 19th century, supercritical solvents were not systematically explored as alternatives to conventional extraction methods until the 1960s.[62] A notable milestone was the pioneering work of Kurt Zosel,[63] who was the first to patent the use of $scCO_2$ for coffee decaffeination.[64] The principle of SFE lies in the unique physicochemical properties of supercritical fluids, which exhibit an intermediate behaviour between that of gases and liquids. Specifically, they combine low viscosity and negligible surface tension, favoring penetration into porous matrices, and a density similar to that of a liquid, which enhances solvation power.[65] These properties can be easily modulated by adjusting pressure and temperature.[66] Among the solvents used in SFE, CO_2 is by far the most commonly employed due to its numerous advantages: it is non-toxic, non-flammable, of low-cost, environmentally benign, and recognized as a safe solvent by the FDA.[67] Additionally, it has a low critical temperature (31.1 °C) and a moderate critical pressure (7.4 MPa), which are conditions easily achievable at both laboratory and industrial scales.[62] Interesting phase behaviour has been described when NADES are used as co-solvents in $scCO_2$ systems.[58,68,69] For instance, studies using hydrophobic terpenoid-based mixtures such as menthol : eucalyptol (ME : EU) or camphor : eucalyptol (CA : EU) demonstrated the formation of a homogeneous liquid phase under typical extraction conditions (*e.g.*, 50 °C and 200 bar).[68,70] This phase homogeneity suggests that $scCO_2$ acts as a solute within the liquid phase, significantly enhancing solvation power and extraction yields for lipophilic compounds.

Conversely, when polar hydrophilic NADES, such as betaine : glycerol, are employed, full miscibility with CO_2 is generally not achieved. Instead, the system exhibits biphasic behavior, in which pressurized CO_2 expands the NADES phase, forming a GXL. This expansion reduces solvent viscosity and enhances mass transfer without leading to a single homogeneous phase.[69] In GXL systems, inert gases such as CO_2 are dissolved into pressurized liquid solvents to enhance extraction performance by modifying the solvent polarity, viscosity, and diffusivity.[71] Accordingly, a wide range of solvent systems can be identified based on the nature of liquid and gaseous solvents and their mutual solubility under high pressure. Considering the use of CO_2 as the expansion gas, three general scenarios may be considered: (i) CO_2 is insoluble or only slightly soluble in the liquid phase, resulting in the formation of two distinct phases (*e.g.*, water); (ii) CO_2 is soluble in the liquid solvent, forming a single phase and promoting considerable physicochemical changes in the solvent (*e.g.*, ethyl acetate); and (iii) the liquid solvent dissolves limited amounts of CO_2, leading to small changes in polarity and volumetric expansion (*e.g.*, crude oil).[72]

A comparable behavior has been reported for CO_2-expanded DES systems applied to the extraction of crocin I from gardenia fruits using a polar DES composed of ChCl : propylene glycol (1 : 3, molar ratio).[73] Phase equilibrium studies revealed the formation of a two-phase system, indicating that CO_2 does not fully mix with the DES. Although crocin I was solubilized exclusively in the DES liquid phase, the presence of CO_2 influenced extraction performance by altering the DES properties through expansion. This effect was evidenced by the increase in extraction yield with rising system pressure (from 4 to 12 MPa). In this context, the system aligns with scenario iii, in which limited CO_2 solubility in the liquid solvent induces volumetric expansion and subtle polarity changes.[72]

Coupling modules

From a process engineering perspective, integrating extraction with downstream separation and analytical units aligns with the broader concepts of process integration and process intensification.[74,75] The complementarity of these concepts refers to strategies that achieve significantly smaller, cleaner, and more energy-efficient processes by combining multiple unit operations, enhancing transport phenomena, or eliminating intermediate handling and transfer steps. In addition to process efficiency, integrated configurations provide significant opportunities for heat and energy integration, particularly when processing high-viscosity DESs. Since DES viscosity is highly temperature-dependent, localized reductions in temperature at module interfaces or during depressurization can cause substantial increases in viscosity.[76,77] This effect can compromise pumpability, hinder mass transfer, and destabilize the entire flow system. Thermally coupled hybrid separations demonstrate that heat integration is a primary mechanism for achieving greater process intensification while reducing energy demand and environmental impact. In DES-based systems, these strategies can simultaneously reduce energy consumption while preserving solvent fluidity, which is essential for high-viscosity formulations.[78]

New possibilities for the development of (semi)continuous biomass valorization processes can be facilitated by combining complementary techniques to generate multiple product streams (Table 1 and Fig. 4). Although still relatively underexplored, the combination of pressurized solvents, mainly DES, with downstream separation methods such as SPE, membrane separation, or liquid–liquid extraction (LLE) has been demonstrated. These integrated options can function as downstream units for extract concentration, fractionation, purification, or clean-up of a given extract. The use of pressurized fluids as extraction media enables efficient integration of downstream separation units. Therefore, PLE, SFE, or GXL extraction are particularly attractive as primary extraction techniques. For instance, when combining PLE with SPE, the particle size and packing density of the SPE adsorbent affect the hydrodynamic resistance of the fluid. This often requires operating at higher pressures to maintain a stable flow rate, which can ultimately result in greater reproducibility. In this context, Chaves *et al.* (2022) demonstrated the effectiveness of an in-line PLE-SPE configuration using conventional green solvents for the valorization of agro-industrial by-products.[79] By processing lemon peels (Citrus limon) with water–ethanol mixtures, the authors achieved simultaneous extraction and fractionation of phenolic compounds. The evaluation of different adsorbents revealed that Sepra™ C18-E allowed efficient separation of polar and less polar compounds into distinct fractions. This approach resulted in high yields of hesperidin and narirutin, outperforming conventional extraction methods in terms of both selectivity and concentration. Moving towards next-generation alternative solvents, de Souza Mesquita *et al.* (2023) developed an innovative PLE-SPE platform combined with DES to recover anthocyanins from Jabuticaba waste (*Plinia cauliflora*).[80] To support solvent selection, the authors initially employed theoretical screening using the COSMO-RS model to predict the solubility of the target compounds. After experimental validation and process optimization, the optimal solvent system was identified as a ChCl : lactic acid mixture (1 : 2, molar ratio) containing 35% (w/w) of water.

The in-line SPE step, using a Strata-X C18 adsorbent, played a fundamental role in selectivity retaining anthocyanins while efficiently removing the eutectic solvent and other co-extracted interferents. This resulted in a high-purity extract with thermal stability superior to that obtained using conventional solvents such as water or ethanol. Overall, this approach proved that PLE-SPE coupling is robust enough to operate with solvents spanning a wide range of viscosities and physicochemical properties, thereby promoting more sustainable and efficient biomass valorization processes. An additional advantage of (semi)continuous extraction systems is their suitability for online coupling, which enables the direct interconnection between the extraction unit with the analytical or separation techniques. This setup allows periodic sampling and analysis of the process effluent without interruption operation or requiring manual handling.[12] As a result, the extraction system evolves into a dynamic analytical platform, enabling real-time monitoring of extraction kinetics, breakthrough behavior, and product composition. Such integrated systems clearly demonstrate how on-line analytical coupling can support process understanding and facilitate the identification of optimal oper-

Table 1 Overview of integrated biomass valorisation systems, highlighting different combinations of extraction techniques, solvent systems, downstream processing strategies, and analytical coupling, along with their respective target compounds or fractions

Biomass	Extraction technique and conditions	Solvent system	Downstream processing	In-line or on-line detection	Target compound(s) or fractions	Ref.
Brazilian berry waste	PLE (90.2 °C, 1500 psi, static time 12.5 min, dynamic time up to 40 min, 1.5 mL min^{-1})	Acidic DES, ChCl : lactic acid (1 : 2, molar ratio, wt% = 35% water), with no solvent recovery	SPE using C18-type adsorbent (Strata-X C18)	None	Anthocyanins	80
Cocoa bean shells	PLE (60 °C, 1500 psi, gradient H_2O → EtOH over 45 min, 1 mL min^{-1})	EtOH : H_2O gradient (from 100% H_2O to 100% EtOH), with no solvent recovery	SPE using polymer-type adsorbent (PoraPak Rxn RP Bulk), with 10 times adsorbent reuse	On-line HPLC–PDA (real-time monitoring of elution and fractionation)	Methylxanthines and phenolic compounds	81
Engineered microalgae *Chlamydomonas reinhardtii*	Continuous membrane-assisted LLE using hydrophobic hollow-fiber contactor (polysulfone, 0.93 m^2, pore size 0.65 μm; culture flow 45 mL min^{-1} shell side; dodecane flow 7.5 mL min^{-1} lumen side; ambient T and P; 60 day continuous operation), followed by in-line Zaiput SEP-10 liquid–liquid phase separation (dodecane/methanol, 2 mL min^{-1} each) and OSN concentration (DuraMem 300, 20 bar)	Dodecane and methanol, methanol was recovered *via* OSN with 100% patchoulol rejection, while dodecane was recovered in the Zaiput separator	Dodecane–methanol liquid–liquid transfer with in-line Zaiput phase separation, followed by OSN for product concentration and solvent recycling	None	Sesquiterpenoid patchoulol	10
Lime industrial waste	Ultrasound-assisted Pressurized Liquid Extraction (UAPLE) (120 °C, 15 MPa, HIUS pre-treatment at 400 W for 5 min, static time 10 min, dynamic time 2 h, 2 mL min^{-1})	Water followed by EtOH : H_2O 50 : 50 (v/v), with no solvent recovery	SPE using C18-type adsorbent (SepraTM C-18-E)	On-line HPLC–UV	Hesperidin	82
Rosemary	Ultrasound-assisted Pressurized Liquid Extraction (UAPLE) (10 MPa, 15 min static + 15 min dynamic, 2 mL min^{-1}; CD optimum: 62.1 °C, 400 W; RA optimum: 100 °C, 240 W)	EtOH 99.5% (v/v) followed by EtOH : H_2O 30 : 70 (v/v), with no solvent recovery	None	In-line UV-vis detection	Carnosic derivatives (CD) and rosmarinic acid (RA)	83
Milk thistle seeds	SFE (pure $scCO_2$ for triglycerides: 40 °C, 25 MPa, 3 mL min^{-1}, 2 min static + 6 min dynamic; EtOH : CO_2 30 : 70 for flavonolignans: 40 °C, 25 MPa, 1.5 mL min^{-1}, 5 min static + 5 min dynamic)	Pure $scCO_2$ followed by EtOH : CO_2 30 : 70 (v/v), with no solvent recovery	None	On-line SFC-PDA detection (UV) coupled to SFC; optional MS compatibility demonstrated in related setups	Non-polar triglycerides and polar flavonolignans	84

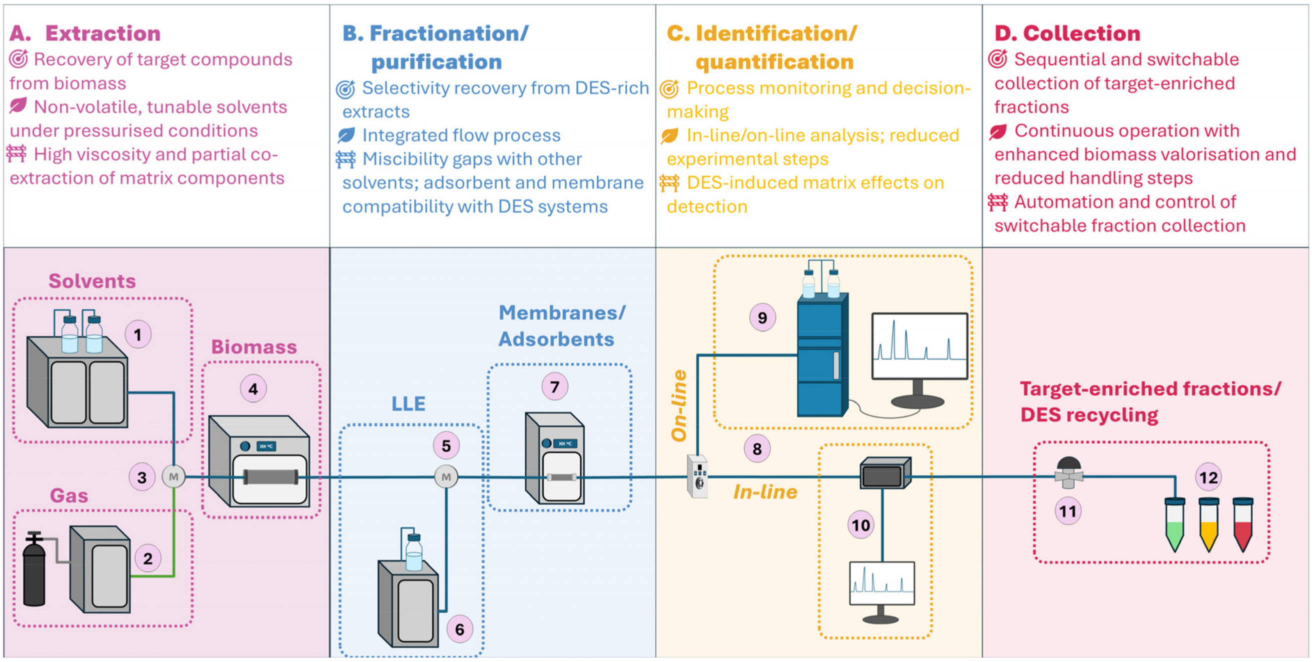

Fig. 4 Schematic representation of the modular and configurable DES-based extraction–fractionation-analysis platform, highlighting alternative operational pathways from pressurised extraction to fraction collection. The extraction section (left) comprises: (1) a liquid solvent pump connected to solvent reservoirs, and (2) a gas supply line (*e.g.*, CO_2 or N_2), enabling operation under supercritical or GXL conditions; (3) a mixing junction where the liquid solvent and pressurized gas are combined to tune solvent properties; and (4) an oven within the extraction cell, in which biomass is processed under controlled temperature and pressure. Downstream of extraction, the system can be coupled to fractionation or purification units. In this stage, (6) a secondary pump introduces a solvent that is miscible or partially miscible with the extraction medium, which (5) is contacted with the DES-rich extract to initiate LLE. Alternatively, or complementarily (7) the extract can be directed through membrane-based or adsorbent-based modules for selective fractionation and purification. The analytical section includes (8) analytical monitoring, which can operate in two distinct modes: (9) on-line, in which discrete aliquots are periodically diverted *via* a sampling loop to a chromatographic system (*e.g.*, HPLC–PDA), enabling compound-resolved identification and quantification at the cost of a time lag determined by the chromatographic cycle (typically several minutes per injection) or (10) in-line, in which the process stream passes continuously through a flow-through detector (*e.g.*, UV-Vis), providing virtually instantaneous feedback with no sampling-induced time lag. System pressure is controlled by (11) a back-pressure regulator, ensuring stable operating conditions throughout the process. Finally, (12) the target-enriched fractions are collected, enabling sequential and switchable recovery of products according to the selected process configuration. Original figure created by the authors. Icons were used as graphical elements under a Flaticon premium license (no attribution required).

ating conditions. In this context, Gros *et al.* (2023) developed an on-line platform for the processing of milk thistle seeds, in which $scCO_2$ extraction was directly coupled to supercritical fluid chromatography (SFC).[84] This approach compared both split and loop transfer modes and exploited on-line chromatographic data to monitor extraction kinetics, quantify defatting time, and characterize triglycerides and flavonolignans within a single automated sequence. Similarly, a gradient PLE–SPE system applied to cocoa bean shells incorporates an in-line sampling loop and a dilution pump to inject the extraction effluent directly into an on-line high-performance liquid chromatography system equipped with photodiode array detection (HPLC–PDA).[81] This configuration enables the real-time generation of elution profiles of theobromine, caffeine, and phenolic compounds, thereby facilitating their effective fractionation. Moreover, it allows direct assessment of SPE performance and reusability without disrupting the pressurized flow. An alternative approach for real-time monitoring involves the use of an in-line UV-Vis or similar detector. In this method, the continuous process stream passes directly through the detector, thereby eliminating the need for periodic aliquot collection. This strategy was effectively demonstrated by Strieder *et al.* (2024) and Pizani *et al.* (2025).[83,85] In the latter study, an ultrasound-assisted pressurized liquid extraction (UAPLE) system was coupled in-line to a UV-Vis detector to monitor the extraction of carnosic derivatives (CD) and rosmarinic acid (RA). Unlike chromatographic methods, the extract is analyzed continuously in the *in-line* mode without passing through a separation column. Although this configuration relies on total absorbance for detection, which may reduce precision compared to offline HPLC due to the absence of compound separation, it provides the significant advantage of delivering immediate feedback on system performance. By switching solvents during the process, from pure ethanol to aqueous ethanol, the authors were able to distinguish the elution profiles of different compound classes in real time, thereby demonstrating the effectiveness of the system for rapid process control without the complexity associated with chromatographic columns. However, when considering DES-based systems, their physicochemical properties impose specific constraints on real-time analytical performance. The inherently high viscosity of DES, particularly at lower temperatures or higher concentrations, may increase backpressure in flow-through detector cells, promote non-uniform flow profiles, and reduce baseline stability in UV-Vis measurements.[54,76] In on-line configurations involving chromatographic or adsorption columns, these limitations become even more critical, as highly viscous DES streams may impair mass transfer, increase the risk of clogging or bed obstruction, and ultimately preventing a stable operation to occur. Moreover, certain DES formulations may progressively thicken under sustained pumping, which can further elevate system pressure, overload or damage pumps and fittings, and compromise or even interrupt the analytical measurement itself.[54] Beyond flow resistance, viscous DES-rich streams can be destabilized during dilution, solvent switching, or localized temperature drops that frequently occur at the interface between process steps. This could potentially trigger precipitation of individual DES components, leading to blockage of tubing, fouling of detector cells, or irreversible damage to chromatographic columns.[86,87] Furthermore, the UV absorbance of DES components may compromise spectroscopic selectivity, needing for the careful selection of detection wavelengths or the implementation of blank-subtraction routines. These factors demonstrate the importance of rigorous stream conditioning and phase management before conducting in-line or on-line analysis.

Besides analytical integration, downstream processing can be further intensified by coupling extraction or conversion steps with membrane-based or liquid–liquid separation techniques.[10,11,55,88] For instance, hollow-fiber membrane contactors offer a high-surface-area interface that enables the continuous transfer of target compounds from fermentation broths into an organic solvent phase without the formation of stable emulsions.[10] A notable application of this configuration is the continuous extraction of patchoulol from engineered *Chlamydomonas reinhardtii*, in which a hydrophobic hollow-fiber membrane contactor facilitated the accumulation of the sesquiterpenoid product in a dodecane solvent.[10]

To further intensify the process and enhance sustainability, these extraction systems can be integrated with Organic Solvent Nanofiltration (OSN) units. In the case of patchoulol production, OSN was employed to separate the product from the solvent, achieving 100% rejection of patchoulol while enabling the recovery and reuse of the dodecane solvent. Furthermore, continuous liquid–liquid separators, which utilize membranes with tailored wetting properties to separate immiscible phases, can be implemented to streamline the separation of aqueous and organic streams following flow biocatalysis.[11] These integrated approaches significantly reduce solvent consumption and improve both the economic and environmental sustainability of bioprocesses, offering clear advantages over traditional thermal separation methods.

Nevertheless, modern approaches can also be employed for generating valuable products more efficiently.[82,89] In this context, coupling PLE with high-intensity ultrasound (HIUS), also known as UAPLE, or adding additional process steps, has demonstrated to be particularly effective. For instance, Santos *et al.* (2025) developed an integrated HIUS-PLE system to maximize the recovery of isoflavones from soybean meal.[89] This hybrid approach exploits acoustic cavitation to disrupt plant cell walls; when combined with the elevated temperatures and pressures characteristic of PLE, it significantly enhances solvent penetration and facilitates the release of target analytes. Demonstrating the versatility of such hybrid systems, Sanches *et al.* (2024) combined HIUS-PLE with in-line SPE and on-line HPLC-UV for the valorization of lime industrial waste.[82] Operating with subcritical water (120 °C and 15 MPa) and high-power ultrasound (400 W), the authors achieved a high recovery of hesperidin while simultaneously enabling extract purification and real-time quantification.

The versatility of these integrated approaches is exemplified by the modular platform shown in Fig. 4, which represents the conceptual shift from isolated extraction units to configurable, flow-driven biorefinery architectures. The schematic demonstrates examples of the range of operational configurations achievable from extraction to collections steps. Depending on the target compounds, solvent properties, and matrix complexity, the extracted stream can be directed to SPE modules for selective purification, membrane-based units for concentration and solvent management, or LLE stages for fractionation based on polarity or miscibility differences. The collection stage is designed as a flexible point, enabling sequential and switchable recovery of target-enriched fractions and, when compatible with solvent stability and system configuration, the recirculation and recycling of DES phases to support solvent circularity during (semi)continuous operation. Nevertheless, the implementation of such integrated systems is constrained by critical operational limitations that must be addressed during the design phase. Challenges such as membrane and adsorbent fouling, chemical incompatibility between DES components and polymeric materials, DES viscosity and their lack of miscibility with other solvents, progressive changes in solvent structure and performance over multiple cycles can compromise long-term stability and process robustness if not adequately managed. The integration of analytical modules serves as the principal function of process control. The distinction between both coupling modes is as follows: (i) in-line detection, in which the entire process stream flows continuously through a detector (*e.g.*, UV-Vis) with no discrete sampling step and therefore negligible time lag, and (ii) on-line detection, in which aliquots are periodically transferred to a chromatographic instrument (*e.g.*, HPLC–PDA or SFC-PDA), introducing a time lag corresponding to each analytical cycle.[12] In-line configurations deliver real-time feedback facilitating rapid process adjustments, although they are more susceptible to spectral interferents. On the other hand, on-line systems achieve compound-specific resolution at the cost of an inherent time lag, primarily due to the duration of chromatographic runs. To mitigate this time lag, shorter and more efficient chromatographic columns can be employed to reduce the duration of each analytical cycle.

These considerations underscore that an integrated platform must be accompanied by rigorous assessment of solvent, material, and process compatibility to ensure that modularity results in efficient, scalable, and sustainable biorefinery systems.

Advantages of in-line systems: a comparative analysis

The transition from batch to flow systems is widely recognized for its operational and efficiency benefits. In this context, we propose a comparative analysis based on previously published work in which a semi-continuous operation could realistically be adopted. The study by Mesquita *et al.* (2024) (Fig. 4A) follows a conventionally structured batch workflow comprising: (i) an initial extraction of anthocyanins using GVL; (ii) a subsequent extraction of ellagic derivatives employing choline acetate ([Ch][OAc]); and (iii) the valorization of the residual biomass into biochar using a ChCl and oxalic acid system (ChCl : OA; 1 : 2, molar ratio).[90] In this process, each extraction step was performed independently in separate vessels, requiring manual loading and unloading of both solvents and biomass between stages. Initially, pomegranate waste was mixed with aqueous GVL (Fig. 5A, A) under controlled temperature and agitation in a stirred reactor (Fig. 5A, 1), enabling the extraction of anthocyanins over a fixed extraction period. The resulting sample was then centrifuged (Fig. 5A, 2). The exhausted solid material was subsequently recovered and transferred to the next extraction stage, an alkaline extraction

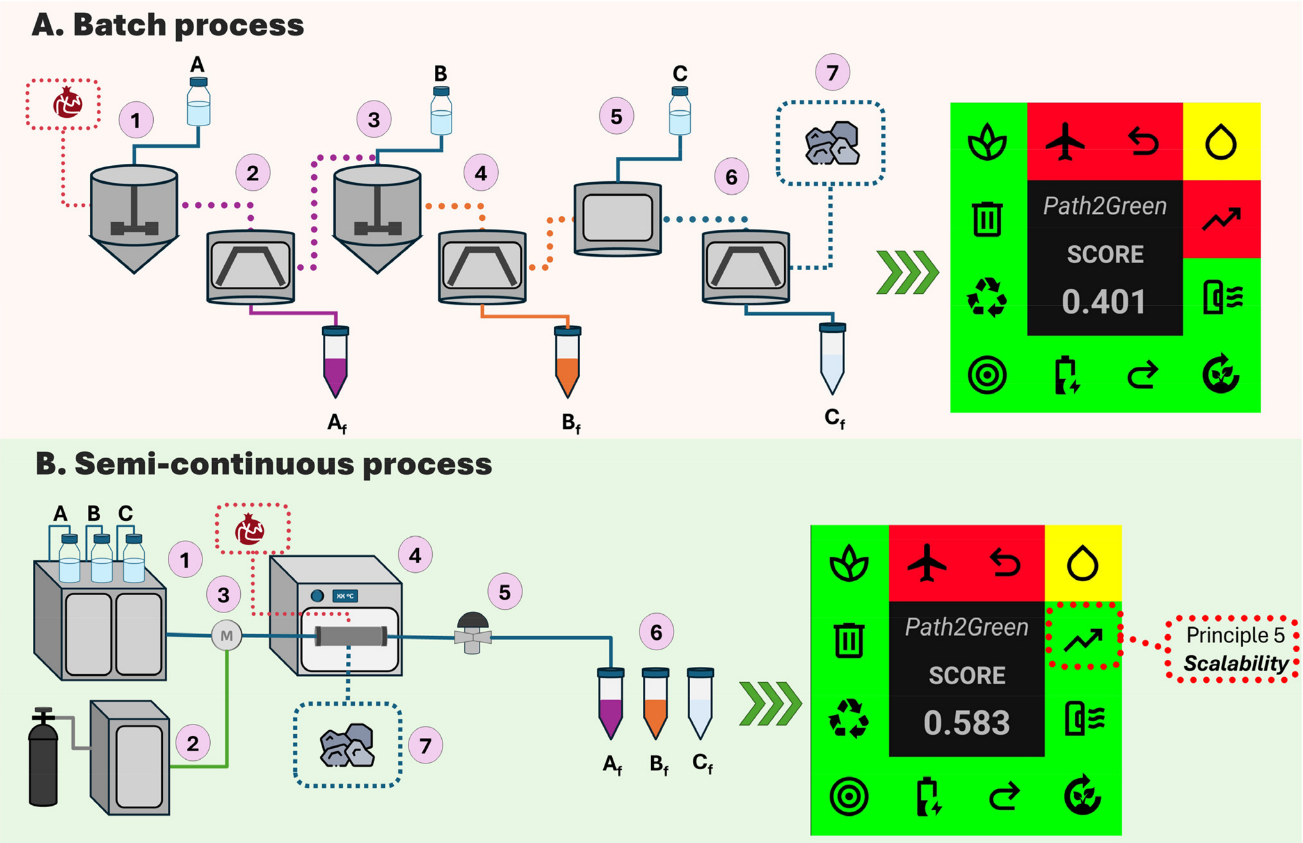

Fig. 5 Schematic representation of the proposed batch (A, top) and semi-continuous (B, bottom) DES-based biorefinery, corresponding to the batch process reported by Mesquita *et al.* (2024).[90] In both configurations, the solvents employed are denoted as A = GVL, B = [Ch][OAc], C = ChCl : OA and the corresponding fractions A_f, B_f, and C_f, corresponding to the anthocyanin-rich fraction (GVL stage), the ellagic acid-rich fraction ([Ch][OAc] stage), and the final biochar-associated fraction (ChCl : OA stage), respectively. For each configuration, the respective Path2Green sustainability score is displayed on the right. The batch process includes the following steps: (1) a stirred reactor in which fresh biomass is mixed with the extraction solvent; (2) a centrifugation unit to separate the solid residue from the liquid extract; (3) a second stirred reactor where the subsequent solvent is added and the extraction procedure is repeated; (4) centrifugation to recover the second extract; (5) a pressurized reactor for mild carbonization; and (6) a final centrifugation step to recover the (7) generated biochar. The semi-continuous process comprises: (1) a solvent pump connected to three solvent reservoirs (A,B, and C), enabling sequential solvent feeding; (2) an inert gas (*e.g.*, nitrogen) pressurization unit for line purging, solvent displacement, and preparation for subsequent extraction stages; (3) a switching junction directing either solvent flow or nitrogen into the system; (4) an oven containing the fixed-bed extraction cell containing pomegranate waste, in which extraction and *in situ* biochar formation are performed within the same unit; (5) a back-pressure regulator to maintain constant operating pressure; (6) collection of the fractions A_f, B_f, and C_f; and (7) solid residue converted into biochar within the extraction cell. Original figure created by the authors. Icons were used as graphical elements under a Flaticon premium license (no attribution required).

(Fig. 5A, 3), where [Ch][OAc] (Fig. 5A, B) was added and kept under agitation to recover ellagic acid derivatives. After extraction, centrifugation was again performed (Fig. 5A, 4) to isolate the ellagic acid–rich fraction (Fig. 5A, Bf). Finally, the twice-extracted biomass was transferred to a dedicated reactor for DES-assisted carbonization (Fig. 5A, 5), in which the ChCl : OA (Fig. 5A, C) eutectic mixture promoted mild *in situ* biochar formation at 120 °C. The resulting solid was recovered after a final centrifugation step (Fig. 5A, 6), yielding the biochar fraction (Fig. 5A, 7) and the recovered ChCl : OA phase (Fig. 5A, Cf).

Although this cascade biorefinery is conceptually robust, its operational mode remains entirely discontinuous, relying on sequential loading and unloading steps, extensive manual handling, and solvent replacement between stages. Within the conceptual framework of this review, centered on the transition from batch DES-based processes toward (semi)continuous systems, such a configuration presents intrinsic limitations that directly interfere on the process intensification, mainly with respect to scalability and step reduction. To systematically evaluate these limitations and to illustrate the gains enabled by a semi-continuous redesign, the comparative discussion that follows is structured according to the sustainability principles defined by the Path2Green metric.[23] Path2Green is a semi-quantitative sustainability metric developed to evaluate biomass extraction processes, proposed by de Souza Mesquita *et al.* (2024).[23] This metric is based on 12 dedicated principles of green extraction that cover the key aspects of an extraction workflow: (1) biomass origin, (2) transport, (3) pre-treatment, (4) solvent selection, (5) scalability, (6) purification, (7) extraction yield, (8) post-treatment, (9) energy consumption, (10) application potential, (11) repurposing of raw materials, and (12) waste management. Each principle is independently scored on a continuous scale from −1.0 (indicating poor adherence) to +1.0 (indicating full adherence), with intermediate values representing partial compliance. The final Path2Green score is computed as a weighted average of the individual principle scores, with default weights reflecting the relative contribution of each principle to three sustainability pillars: environmental (weight 3), social (weight 2), and economic (weight 1). Nevertheless, these weights can be adjusted by the user to emphasize a specific sustainability pillar according to the context or strategic focus of the assessment. A final score near +1.0 reflects strong alignment with sustainable extraction practices, while negative values indicate significant sustainability deficiencies that may necessitate process redesign. Results are presented using a color-coded pictogram, with green, yellow, and red representing high, neutral, and poor adherence, respectively, to provide a rapid diagnostic of process performance across all 12 dimensions. While Path2Green does not replace a comprehensive LCA, it provides a practical screening tool for the strengths and critical shortcomings of a given extraction process.

First, the sequential extraction steps described by Mesquita *et al.* (2024) can be re-engineered into a semi-continuous fixed-extraction cell configuration.[90] As depicted in Fig. 5B, the pomegranate waste is packed into a pressurized extraction cell (Fig. 5B, 4) and remains static throughout the entire process. In this setup, an aqueous GVL solution is pumped (Fig. 5B, A) through the column at a controlled flow rate, allowing anthocyanins to be eluted continuously without requiring agitation or periodic solvent replacement. Once the biomass becomes depleted in anthocyanins, the system can be switched directly to the second extraction stage, while an optimal anthocyanin fraction would be recovered (Fig. 5B, Af). To prepare the system for this transition, an inert nitrogen stream (Fig. 5B, 2) is passed through the extraction cell to displace residual solvent from the vegetal matrix. This process maximizes solvent recovery and ensures effective clean-up, providing optimal conditions for the next extraction step.

Subsequently, the same extraction cell is flushed with a controlled stream of [Ch][OAc] (Fig. 5B, B), enabling the extraction of ellagic acid derivatives from the same solid matrix without any manual unloading or reloading of biomass. This operational continuity eliminates downtime, reduces process variability, and supports a modular framework in which each solvent phase is collected in its respective target fraction (Fig. 5B, Bf).

Finally, an *in situ* biomass-to-biochar conversion step is performed using the ChCl : OA (Fig. 5B, C). In contrast to batch reactors, which require repeated opening, cleaning, reloading, and reheating before each cycle, the DES-assisted carbonization is performed within the same pressurized extraction cell (Fig. 5B, 4) used for both preceding extraction stages. Following the sequential GVL and ChOAc extractions, the exhausted biomass remains confined within the extraction vessel, which is subsequently flushed with the ChCl : OA mixture and heated to 120 °C under static conditions. The resulting biochar (Fig. 5B, 7) can be cleaned *via* a nitrogen-pressurized purge prior to recovery, while the ChCl : OA phase is simultaneously recovered (Fig. 5B, Cf) and reused.

This process redesign is expected to yield improved Path2Green sustainability scores, mainly for principle 5 (scaling), owing to the transition from a fully batch to a semi-continuous configuration. The detailed input parameters, scoring justifications, and weights adopted for each Path2Green principle are provided in SI (Table S1). These scores are sensitive to the assigned weights and the qualitative judgments for each principle. Consequently, the absolute values should be regarded as indicative, with the primary utility of the metric being comparative scenario analysis, such as batch *versus* semi-continuous processes.

Specifically, the score for principle 5 increases from −1 to +0.50, resulting in a final score improvement from 0.401 in the original batch configuration to 0.580 in the proposed semi-continuous approach. Additional advantages are anticipated, even if not explicitly quantified by the Path2Green framework. Notably, the semi-continuous configuration is expected to reduce solvent demand, as improved mass-transfer conditions can be achieved under flow-through extraction.[7,91] Consequently, both energy and solvent consumption are reduced, resulting in a more cost-effective process. While the proposed redesign offers clear sustainability and efficiency gains, its implementation would require validation at pilot scale, particularly regarding pressure stability, long-term solvent recyclability, and biomass heterogeneity.

Although extract quality is not directly quantified by sustainability metrics, it is also likely to enhance under semi-continuous conditions. Reduced solvent volumes lead to more concentrated anthocyanin- and ellagic acid-rich fractions, while tighter control of extraction kinetics enables more precise fractionation. Moreover, the modular nature of the proposed configuration facilitates the integration of dedicated downstream purification units, such as membrane concentration, SPE modules, or liquid–liquid fractionation, further improving product purity and allowing efficient recovery and recirculation of both GVL and choline-based solvents.

Quantitative head-to-head comparisons of batch and semi-continuous operation are scarce for DES-based extraction. However, evidence from related biomass processing fields consistently shows that switching from batch to flow improves key process metrics. In aqueous acetone organosolv fractionation of lignocellulosic biomass, Smit *et al.* (2024) showed that a counter-current semi-continuous design, compared to batch-wise operation under equivalent severity, increased C5 sugar yields from 82% to 92%, improved feedstock delignification from 78% to 82%, and simultaneously reduced sugar degradation to furfural from 7.8% to 4.6%.[92] Notably, the isolated lignin retained a higher β-O-4 content (20 *vs.* 14 per 100 aromatic units) and exhibited less condensation, indicating that reduced residence time of solubilized products in the hot liquor preserved product quality, a principle directly transferable to thermally sensitive bioactives in DES-based extraction. In hydrothermal liquefaction of lignocellulosic feedstocks, Wang *et al.* (2023) reported that continuous-flow operation at 300 °C increased biocrude yields by 21–36% relative to batch processing (*e.g.*, 34.5 *vs.* 28.5 wt% for pinewood), while reducing solid residue formation by more than half and improving energy recovery from 50.8% to 52.0%.[93] The authors attributed these gains primarily to the shorter effective residence time in the continuous reactor, which limited repolymerization of reaction intermediates. This process represents a degradation pathway analogous to the thermal degradation of phenolics or anthocyanins observed during prolonged batch DES extraction. Similar trends were observed in semi-continuous hydrothermal carbonization, where Heidari *et al.* (2022) demonstrated that direct exposure of biomass to reaction conditions, bypassing the gradual heating ramp characteristic of batch operation, increased the carbon content of the resulting hydrochar by approximately 3%, improved its heating value by 2.15 MJ kg^{-1}, and reduced the required heating time from 38 to 8 minutes at 260 °C.[94] Although these examples originate from thermochemical and biochemical conversion platforms rather than DES-based solvent extraction, the fundamental engineering rationale persists unchanged. Continuous solvent renewal can increase mass-transfer driving forces, while shorter product residence times reduce degradation and secondary reactions. Integrated downstream processing supports prolonged, stable operation and enhances product recovery, with potential for broader application and higher purity. Establishing quantitative benchmarks such as throughput, solvent-to-feed ratio, solvent recovery rate, energy demand per unit of extract, and fraction purity under controlled DES-based batch and semi-continuous conditions is essential to validate the process intensification claims presented in this perspective.

Despite these advantages, semi-continuous systems also present specific challenges, particularly when processing complex biomass matrices and viscous or structurally diverse solvents such as DES. Stable flow through a packed extraction bed requires precise control of particle size distribution and bed compaction to prevent pressure fluctuations, channelling, or clogging.[80] These issues are generally less critical in batch systems. In addition, the high viscosity of DES may hinder pumpability, often requiring auxiliary heating to ensure consistent flow.[95]

Solvent switching between extraction stages must also be precisely managed to avoid unwanted co-extraction, as biomass contains interferents that can be undesirable for correct fractionation. Furthermore, integrating downstream purification modules in semi-continuous formats also requires careful synchronization of flow rates and operating pressures. Adequate synchronization is mandatory in fractionation procedures, as even minor mismatches between extraction and downstream steps can compromise fraction purity, reduce separation selectivity, and lead to cross-contamination between target fractions.

In addition, prolonged operation may promote particle attrition and the generation of fines, particularly when processing heterogeneous or mechanically fragile biomass, which can progressively reduce bed permeability and increase pressure drop. Over extended extraction cycles, gradual bed compaction may further intensify these effects, leading to channel formation, uneven solvent distribution, and declining mass-transfer efficiency. To mitigate these limitations, continuous-flow systems should incorporate solids-management strategies such as biomass sieving, tighter particle-size control, dilution of the extraction bed with inert materials, and the use of outlet frits or retaining elements to reduce fines migration.[60,96] Additional protection may also be required, including in-line filters and guard cartridges positioned before the back-pressure regulator or analytical unit.[97] The extent to which each of these precautions is required strongly depends on the nature of the biomass processed, as well as on the target compounds or fractions to be selectively recovered.

Furthermore, downstream separation units are also vulnerable, as residual DES components, often characterized by high viscosity and strong intermolecular interactions, may accumulate on SPE media or membrane surfaces, resulting in fouling and reduced separation performance. Hence, cleaning-in-place remains a significant challenge, since DES residues may not be readily removed using conventional aqueous or organic cleaning protocols, thus requiring the development of tailored cleaning strategies and DES-compatible materials to ensure long-term operational stability. Overall, while semi-continuous DES-based biorefineries offer advantages in scalability, reproducibility, and alignment with green chemistry and sustainability metrics, their successful implementation ultimately depends on optimized reactor design, robust process control, solvent–matrix compatibility, and a favorable techno-economic balance.

Conclusions and critical analysis

This review has examined recent advances in DES-based extraction with a particular focus on process design, intensification strategies, and the transition from batch to (semi)continuous operation. While DES are frequently described as green solvents, the analysis presented here reinforces that their sustainability is not intrinsic but highly dependent on solvent recovery, energy intensity, and operational configuration. When these factors are explicitly considered, DES-based systems can offer meaningful advantages in terms of selectivity, solvent tunability, and integration potential within biorefinery concepts.

The comparative assessment of batch and semi-continuous configurations illustrates that process intensification, rather than solvent substitution alone, is central to unlocking the full potential of DES. Semi-continuous operation enables improved mass transfer, reduced solvent consumption, enhanced fractionation control, and better alignment with sustainability metrics, provided that scale-dependent challenges are adequately addressed. However, batch systems remain relevant for early-stage development and complex matrices, highlighting the need for a pragmatic, application-driven approach rather than a universal process paradigm.

Ultimately, the successful deployment of DES-based extraction technologies will depend on the convergence of solvent chemistry, engineering design, and sustainability assessment. By combining standardized reporting, critical benchmarking, and validated scale-up strategies, future research can move beyond proof-of-concept demonstrations toward robust, economically viable, and environmentally sound processes.

From an implementation perspective, most DES-based extraction and fractionation systems discussed in the current literature remain within TRL 2–4, largely confined to laboratory-scale proof-of-concept studies with limited validation of long-term operation, solvent recirculation, pumpability, fouling control, and materials compatibility. Progress toward TRL 5 will depend on pilot-scale demonstrations under extended operation, particularly for semi-continuous configurations integrating extraction with downstream processing modules. In selected high-value applications, especially where feedstocks are relatively homogeneous and product streams justify higher process complexity, advancement toward TRL 6 may be feasible in the medium term. However, TRL 7–8 remains premature for most integrated DES-based biorefinery platforms, as industrial deployment will require robust techno-economic and life-cycle validations, regulatory acceptance of DES-derived products, reliable solvent circularity, and sustained operation under industrially relevant conditions.

In this context, DES-based (semi)continuous systems represent not a wholesale replacement of existing methodologies, but a complementary and increasingly important pathway toward sustainable biomass valorization. It is a disruptive reconfiguration of how green extraction processes are conceived, integrated, and scaled. By replacing or at least reducing static apparatus-based modes, which remain common despite their limitations at laboratory scale, in favor of pressurized, flow-driven architectures, the entire workflow from solvent–matrix contact to product purification is reconceived as a dynamic, modular, and responsive system. This transition dismantles traditional bottlenecks, meaning: (i) solvent saturation no longer dictates the endpoint; (ii) manual transfers no longer fragment workflow integrity; and (iii) offline analytics no longer delay critical decisions. As a result, process precision improves, and degradation and losses of bioproducts are significantly reduced.

Coupling PLE, SFE, or GXL platforms with downstream units, mainly SPE, membrane contactors, or liquid–liquid separators, creates an end-to-end biorefinery pipeline where extraction, fractionation, and concentration occur in a single pressurized continuum-mode. Real-time monitoring *via* in-line UV-Vis or on-line HPLC-PDA transforms the process from empirical to predictive, enabling termination at the exact moment of optimal yield and minimizing unnecessary solvent and energy use.

The emergence of the MINACs (Mixtures based on Natural Compounds) concept further disrupts rigid thermodynamic definitions by prioritizing functional performance over formal classification. Whether water-modified, viscosity-tuned, or polarity-engineered, these solvents are selected for what they do, not what they are.

The growing body of literature on DES highlights their versatility and potential as alternatives to conventional organic solvents for biomass extraction and fractionation. Nevertheless, a critical examination of existing studies reveals that many reported advantages remain strongly context-dependent and are frequently evaluated under conditions that limit direct comparison. Variations in solvent composition, water content, viscosity, solid-to-liquid ratio, extraction time, and temperature are often introduced simultaneously, making it difficult to isolate the contribution of DES chemistry from that of process design. As a result, reported extraction yields and selectivity data should be interpreted cautiously, particularly when sustainability claims are extrapolated beyond laboratory scale.

A recurring limitation in literature is the implicit assumption that solvent innovation alone is sufficient to deliver greener processes. In practice, the environmental performance of DES-based systems is largely dictated by solvent recovery efficiency, energy demand, and operational mode. Batch extraction remains dominant due to its simplicity and robustness, yet it inherently limits scalability and solvent reuse, especially for viscous or highly structured solvents. Conversely, while (semi)continuous and integrated systems offer clear

Table 2 Comparative overview of batch and (semi)continuous operational modes for DES-based biomass valorization systems

Aspect	Batch	(Semi)continuous
Mass and heat transfer	Often limited by challenges on homogeneous mixing, slower renewal of concentration gradients, and less uniform heat distribution	Typically improves mass and heat transfer through continuous phase movement, enhanced heat exchange, and easier heat integration, although performance may still be constrained by channeling, pressure drop, residence time dispersion, bed heterogeneity, or clogging/fouling phenomena
Process efficiency	Extended processing times and declining mass-transfer driving forces over the course of each cycle tend to reduce the overall process efficiency	Enhanced solvent–matrix interactions and continuous driving forces promote higher yields and shorter processing times, assuming optimal flow and transfer conditions are maintained
Operational control and reproducibility	More dependent on cycle-to-cycle consistency, repeated start-up and shutdown steps, and discrete handling operations, which may increase run-to-run variability.	Supports precise multi-parameter control with enhanced reproducibility. However, greater operational complexity arises from the need to manage a wider set of interdependent process variables
Scalability	Scale-up usually depends on increasing vessel or process unit size, which may exacerbate heat- and mass-transfer limitations	Numbering-up offers a direct scale-up pathway that preserves laboratory-scale transfer regimes, but operational validation at pilot scale remains limited, particularly for viscous DES systems.
Integration of sequential steps	Sequential operations remain compartmentalized, requiring offline product recovery and reconditioning between each processing stage	Enables the integration of sequential operations, including extraction, reaction, fractionation, solvent switching, and other steps, within a unified platform
Monitoring and process analytics	Monitoring is typically restricted to off-line analytical characterization, with no real-time feedback to guide process decisions	More compatible with in-line or on-line monitoring, enabling data-driven adjustment and tighter process control
DES-related operational constraints	Agitation can often reduce high viscosity, but mixing and heat transfer may still limit process efficiency	High viscosity, limited pumpability, unfavorable phase behavior, fouling, solids accumulation, and inadequate solvent compatibility with auxiliary units can restrict long-term operational performance
Solids handling and phase management	Better suited to heterogeneous feedstocks, variable particle size, and systems with solid formation or evolving phase behavior	More demanding when solids, precipitates, biomass fines, or unstable multiphase behavior are present, requiring careful engineering design
Equipment and implementation complexity	Simpler equipment, lower initial capital demand, and easier adaptation during exploratory studies	Requires more specialized hardware and control architecture, increasing implementation complexity and capital cost
Most suitable use cases	Screening studies, exploratory process development, heterogeneous feedstocks, and operations requiring flexibility	Process intensification, integrated valorization cascades, feedstocks with lower variability, and workflows targeting continuous or semi-continuous manufacturing

advantages in terms of reproducibility and intensification, they introduce new challenges related to pressure stability, solids handling, solvent switching, and long-term operational reliability. These trade-offs are rarely quantified in a systematic manner.

The increasing interest in process integration and hybrid extraction–separation schemes further underscores the need for caution. Integration does not necessarily equate to intensification, and in some cases may increase energy consumption or solvent losses if not carefully optimized. Similarly, emerging artificial intelligence (AI)-assisted approaches for solvent and process selection are promising but remain constrained by limited and non-standardized datasets, underscoring the continued importance of experimental validation. Overall, the field would benefit from a stronger emphasis on quantitative benchmarking, critical comparison, and transparent reporting to ensure that advances in DES chemistry translate into genuine process improvements.

Table 2 presents a structured side-by-side comparison of batch and semi-continuous operational modes across 10 relevant aspects to DES-based biomass extraction. The relative significance of each advantage or limitation depends on the specific combination of solvent system, feedstock, target application, and scale. Consequently, these factors should be evaluated individually for each context.

Future perspectives

DES have opened new opportunities for sustainable biomass extraction and fractionation; however, their long-term impact will depend less on solvent novelty and more on rigorous process design, validation, and integration. Soon, progress in this field will require a shift from exploratory solvent screening toward standardized, comparable, and quantitatively assessed extraction systems. Establishing minimum reporting requirements, covering solvent composition and water content, viscosity at operating conditions, solvent recovery efficiency, and energy demand, will be essential to enable meaningful comparison across studies and to prevent overestimation of sustainability claims. Direct benchmarking of batch and (semi) continuous configurations under identical conditions is particularly needed to clarify when process intensification genuinely improves environmental and operational performance. In parallel, systematic evaluation of heat and energy integration within coupled DES-based extraction–separation systems should be prioritized. This consideration is especially significant for systems utilizing high-viscosity DES, as moderate temperature reductions between process stages can result in substantial viscosity increases that negatively affect flow stability, pumpability, and mass-transfer efficiency. Quantifying the potential for internal heat recovery and designing thermally integrated module layouts to prevent viscosity-induced operational failures are essential for accurately assessing the energy footprint of these platforms and ensuring long-term process robustness during semi-continuous operation.

At the medium-term horizon, the focus must transition toward scale-up and process integration. Pilot-scale demonstrations of continuous or semi-continuous DES-based extraction, coupled with in-line separation and solvent recovery units, will be critical to assess operational stability, mass-transfer limitations, and long-term solvent recyclability. At this stage, techno-economic analysis and streamlined LCA should become integral to process development, guiding design decisions and identifying trade-offs between energy consumption, solvent losses, and equipment complexity. Concurrently, engineering challenges related to the handling of viscous solvents, such as pumpability, material compatibility, and fouling, must be addressed through the development of DES-compatible hardware and robust process control strategies.

In the longer term, advances in data-driven methodologies, including AI-assisted solvent and process design, may enable the co-optimization of solvent systems and extraction conditions tailored to specific biomass feedstocks. Moreover, while COSMO-RS provides thermodynamic grounding, machine learning (ML) models trained on experimental datasets can predict extraction yields, solute–solvent affinities, and even downstream behavior (*e.g.*, SPE retention and membrane permeability) as a function of solvent composition, temperature, flow rate, and matrix properties. Nevertheless, such approaches will require high-quality, standardized datasets and extensive experimental validation to ensure transferability across diverse matrices. Ultimately, the successful deployment of DES-based technologies will depend on their integration into next-generation biorefineries operating under steady-state conditions, supported by efficient solvent recovery loops and circular solvent manufacturing frameworks. Regulatory acceptance of DES-derived extracts, particularly for food, cosmetic, and pharmaceutical applications, will also play a decisive role in enabling industrial implementation. Indeed, while DES-based (semi)continuous systems are unlikely to fully replace batch extraction in the near term, they represent a critical pathway toward scalable, data-driven, and genuinely sustainable biomass valorization, if claims of greenness are consistently supported by quantitative metrics and validated at relevant scales.

Conflicts of interest

There are no conflicts to declare.

Data availability

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

Supplementary information (SI) is available. The Supplementary Information includes detailed scores for each principle according to the Path2Green metric for the example discussed in the topic 'Advantages of in-line systems: a comparative analysis'. See DOI: https://doi.org/10.1039/d6gc00798h.

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