Green Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Green Chem.*, 2026, **28**, 7354

Sustainability impact for extraction (SIX Score): from concepts and principles to impact-based metric for green extraction assessment

Giorgio Capaldi, [a] Clelia Aimone, [a] Giorgio Mongardi, [b] Emanuela Calcio Gaudino, [a] Giorgio Grillo *[a] and Giancarlo Cravotto [a]

Received 28th December 2025,
Accepted 8th April 2026

DOI: 10.1039/d5gc07041d

rsc.li/greenchem

The shift towards a circular and sustainable economy has positioned the biorefinery sector as a key player in the valorisation of industrial by-products, particularly through the extraction of bioactive compounds from agri-food residues. Since its introduction in 2012, the concept of Green Extraction (GE) has established a set of principles aimed at process intensification, reducing energy consumption, minimising of solvent use, and mitigating environmental and safety impacts. Despite the widespread adoption of green chemistry and green engineering approaches, a significant gap remains in the availability of quantitative, accessible, and standardized tools for assessing the sustainability of extraction processes. While life cycle assessment offers a comprehensive evaluation framework, its complexity, cost, and data requirements often limit its routine application, especially during early-stage process development. To address this, the article proposes the SIX Score, a simplified sustainability metric that uses the widely recognized six GE principles as formal reference: 1. raw material renewability, 2. solvent hazardousness, 3. energy efficiency, 4. process robustness, 5. waste production, and 6. extract quality. This framework aims to standardize sustainability evaluations, enabling informed decision-making and facilitating iterative improvements in extraction protocols. The tool, embedded in open-access software (SIX Score Hub), is designed to support the continuous optimization of extraction procedures, fostering scientifically grounded advancements in green technologies and sustainable practices. The manuscript will delve into the application of the chosen criteria of the SIX Score in different extractions scenarios considering different technologies and approaches to highlight its applicability, criticisms and main advantages over traditional green metrics systems. By offering a pragmatic and scientifically grounded evaluation system, the proposed framework aims to provide a solid foundation for the scientific community to further refine, expand, and advance the concept of sustainable extraction.

Green foundation

1. We developed the Sustainability Impact for Extraction Score (SIX Score), a formalism-based quantitative metric based on the six principles of green extraction. It standardizes sustainability evaluation by combining process efficiency and safety indicators, enabling objective comparison and continuous improvement toward more sustainable extraction practices.
2. To address gaps in previous methodologies, new quantitative indicators and calculation methods were introduced to ensure a comprehensive, data-driven evaluation of extraction processes, validating the outcome with real case studies. To maximize accessibility, the SIX Score is additionally implemented in open-access software, conceived as an operational wrapper that enables broad dissemination and user-friendly application.
3. Further research will leverage the software's data collection system to (i) refine the metric sustainability benchmarks, (ii) establish an open-access dynamic library of extraction technologies, and (iii) include data-driven guidance functionalities that translate benchmark trends into targeted improvement suggestions.

[a] *Department of Drug Science and Technology, Università di Torino, Via Pietro Giuria 9, 10125 Turin, Italy. E-mail: giorgio.grillo@unito.it*
[b] *Department of Control and Computer Engineering (DAUIN), Politecnico di Torino, Corso Duca degli Abruzzi 24, 10129 Turin, Italy*

1. Introduction

1.1. Green extraction

Extraction is a fundamental separation process by which specific molecules or classes of compounds are isolated from complex matrices, including plant tissues, microorganisms, minerals, industrial residues, and environmental samples. From flavours and fragrances to metals, fuels, and pharmaceuticals, extraction transforms raw and heterogeneous materials into usable resources, making it one of the most enabling operations in science and industry.

This atavistic technique already employed by ancient civilizations to obtain fragrances, medicines, and cooking ingredients has, over the past two decades, progressively expanded beyond conventional approaches such as maceration, percolation, and distillation toward methods often referred to as green extraction (GE), with the objective of improving process efficiency and extraction performance.[1] These emerging strategies explore, among other approaches, the use of enabling technologies, such as ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE) pulsed electric fields (PEF), flow systems and enzymatic approaches, together with alternative solvents, typically derived from renewable and non-petroleum-based sources.[2–6] Examples of such solvents include pressurized liquids (notably supercritical CO_2 and subcritical water) as well as bio-derived ones, such as natural deep eutectic solvents (NaDES), cyclopentyl methyl ether (CPME), and 2-methyltetrahydrofuran (2-MeTHF), though the spectrum is much broader.[7] Although many of these approaches remain limited to laboratory or pilot-scale applications, they offer promising avenues for enhancing extraction efficiency while reducing energy demand, solvent consumption, and environmental impact, thus contributing to the development of more sustainable and scalable extraction processes. The intellectual foundations of this transition can be traced back to 1998, when Anastas and Warner formulated the twelve principles of green chemistry, providing a pioneering framework for embedding sustainability within the chemical sciences.[8,9] Building on this groundwork, Chemat, Abert-Vian, and Cravotto articulated the six principles of GE in 2012.[10] These principles advocate for reduced resource and energy consumption, limited solvent use, decreased environmental burdens, and greater safety, serving as guiding criteria for the redefinition of process intensification in this field.

Despite their strong conceptual relevance, these six principles remain predominantly qualitative. The lack of accessible and standardized quantitative methodologies for sustainability assessment continues to hinder the systematic evaluation and comparison of innovative extraction protocols. Currently, life cycle assessment (LCA) is the most comprehensive and robust tool for evaluating environmental sustainability, as it provides an integrated score accounting for impacts across the entire life cycle of a product, typically adopting a "cradle-to-grave" perspective.[11] This approach has already been applied both in the pharmaceutical industry to drug production and in the more specific sector of GE.[12,13] However, its high costs, extended processing times, and need for extensive datasets and specialized expertise pose barriers to widespread use, especially at lab-scale.[11] On the other hand, simpler green metrics, such as *E*-factor and atom economy, pose some limitation in evaluating with a holistic perspective the sustainability theme, not (or partially) calculating important factors such as energy and time consumption, together with the hazardousness of the process.[14] To address these limitations, we propose the Sustainability Impact eXtraction Score (SIX Score), a novel and easy-to-use green metric that enables rapid and quantitative assessment of the sustainability of extraction processes. Process-efficiency descriptors are combined with safety- and risk-relevant indicators, paving the way to standardization which enables objective benchmarking and supports continuous improvement during process development. The assessment output is expressed as a percentage of greenness, derived from the evaluation of six main criteria, each reflecting a key aspect of the GE principles: 1. raw material renewability, 2. solvent hazardousness, 3. energy efficiency, 4. process robustness, 5. waste production, and 6. extract quality. These criteria, defined as Elemental Factors (EFs), are further articulated into specific subcategories designed to support quantitative assessment and comparative analysis. This framework introduces new indicators to systematically identify optimal extraction parameters, addressing methodological gaps in existing approaches by combining the practicality of simple metrics with a holistic perspective. By enabling direct comparison among different extraction strategies, it supports iterative process optimization and facilitates the identification of targeted improvement opportunities. Moreover, by grounding sustainability claims in measurable and clearly defined criteria, the approach contributes to minimizing the risk of greenwashing and promotes a rigorous, evidence-based evaluation of green extraction processes.

The SIX Score has been implemented in a user-friendly, open-access software that require readily accessible input data and providing easily interpretable outputs. The SIX Score Hub (v.1.0),† conceived as an operational wrapper encourages the integration of sustainability evaluation into process design, fostering more responsible and informed development of green extraction protocols, weighting the impact of technologies and solvents as well. Looking ahead, the platform's data-collection will be used to refine sustainability benchmarks over time, build an open-access dynamic library of extraction technologies. This ready-to-use library will also promote data sharing, dissemination of research outputs, and collaboration within the scientific community. As the transition to green chemistry represents a global challenge, the SIX Score aims to support this effort by providing an accessible methodology for sustainability assessment while fostering collaboration and knowledge exchange across the chemical community through the networking opportunitiesoffered by the platform.

The present work builds upon a comprehensive review of the state-of-the-art of green metrics and their relevance to GE. Thus, the context for SIX Score development has been established, highlighting its key distinctions from existing sustainability assessment tools. This is followed by a detailed discussion of each EF, including its rationale and the underlying

† Direct link to SIX Score Hub v.1.0: https://blankto.github.io/SixScore/

mathematical model. Finally, to further demonstrate SIX Score application, the SI includes real case studies illustrating the tool's applicability under different experimental conditions.

1.2. Evolution of green metrics: towards sustainability quantification in extraction

The first attempt to measure sustainability in organic chemistry was made with the introduction of two complementary green metrics in the last decades of the Twentieth Century: atom-economy (AE) and *E*-factor.[15,16] AE, designed by Trost *et al.*, considers the efficiency of chemical reactions incorporating reactants into the desired product.[15] A high AE indicates that most of the starting materials are integrated into the final product, reducing the formation of by-products. On other hand, the *E*-factor complements the atom economy by accounting for the actual waste generated during a chemical process. The *E*-factor incorporates the chemical yield and includes reagents, solvents, process aids, and in some cases, even fuel, though water is typically excluded from the calculation to avoid distortions in waste quantification.[16] *E*-factor offers a comprehensive perspective on process efficiency and waste management, making it particularly useful in pharmaceutical protocols, demonstrated to be appliable also in up-scaled and in continuous systems.[17] These two methods are the precursors of a range of metrics that evaluate total mass efficiency from various perspectives and are collectively known as mass-based metrics. Metrics like Process Mass Intensity (PMI) and Process Mass Efficiency (PME) expand the analysis to consider the mass of all inputs, including water.[18,19] More specialized metrics, such as Reaction Mass Efficiency (RME) and Effective Mass Yield (EMY), emphasize specific components like carbon atoms or non-benign materials.[20,21] These are just a few examples of mass metrics; however, several reviews and dedicated collections have addressed this highly topical area, including contributions on green chemistry methods, models, and metrics, sustainability indicators for chemicals management, and frameworks for safe-and-sustainable-by-design chemicals and materials.[22–24]

The distinctions among mass-based metrics make them complementary and valuable for evaluating specific aspects of process efficiency; however, do not provide a holistic sustainability assessment. A more comprehensive evaluation should also account for the nature of generated wastes, material hazardousness, as well as energy and time consumption. In this framework, mass metric can be implemented with a more comprehensive evaluation with the application of the so-called impact-based metrics (Fig. 1).[25] These metrics represent an evolution of traditional mass-based indicators, as they explicitly incorporate environmental impact considerations into sustainability assessments.[26] This approach is captured by eqn (1), where P is the impact potential of a substance, I is the environmental impact index, and m is the mass of the substance released as waste or fugitive emissions.

$$I = P \cdot m \tag{1}$$

By integrating both mass flow and impact potential, these kinds of metrics provide a more comprehensive evaluation of a process's environmental footprint. This approach represents an evolution developed over the past twenty centuries, with numerous validated methodologies documented in the litera-

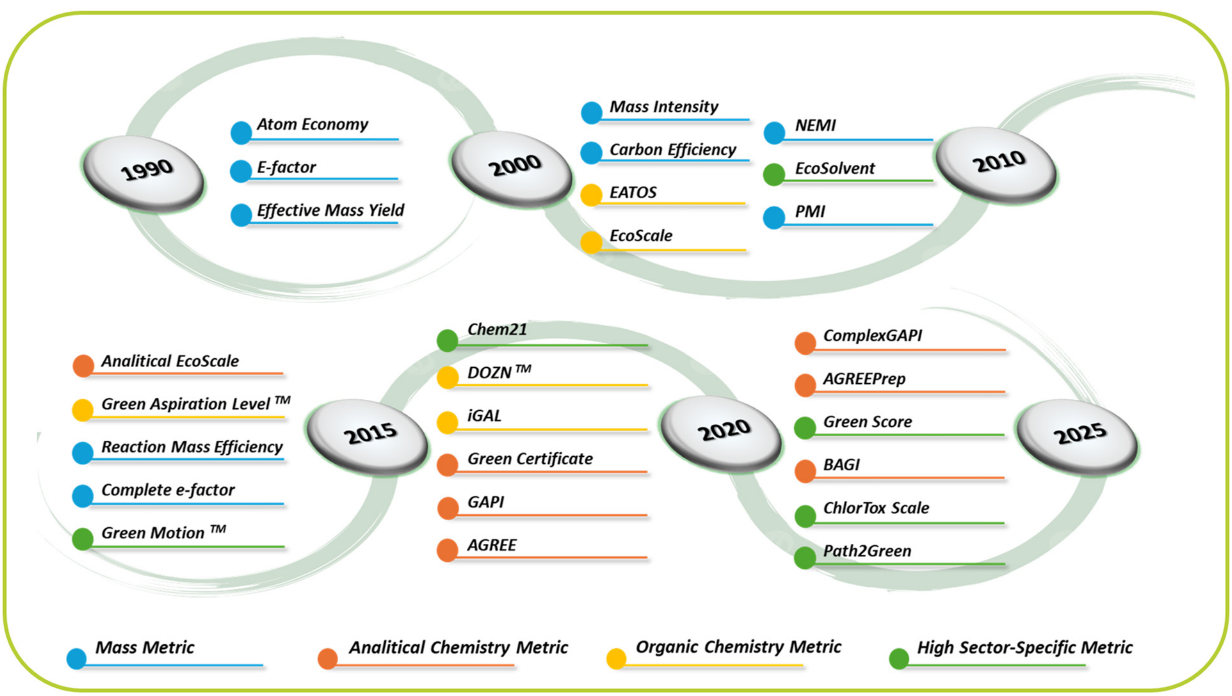

Fig. 1 Evolution of green metrics: timeline.

ture, designed to be applied in specific chemical sectors (Fig. 1). In organic chemistry, metrics such as Environmental Assessment Tool for Organic Syntheses (EATOS), ECOSCALE, DOZN™ and innovation green aspiration level (iGAL) and improved iGAL (iGAL 2.0) have been proposed, offering broader perspectives beyond traditional mass-based metrics.[27–31] Similarly, green analytical chemistry has introduced numerous metrics with a more holistic approach, including Green Certificate, National Environmental Method Index (NEMI), analytical Eco-scale, Green Analytical Procedure Index (GAPI), Analytical Greenness calculator (AGREE), Complementary Green Analytical Procedure Index (ComplexGAPI), Analytical Greenness metric for sample preparation (AGREEprep), Blue Applicability Grade Index (BAGI), and Red analytical performance index (RAPI).[32–40] Additionally, sector-specific metrics such as EcoSolvent, Chem21, and ChlorToxScale are used to assess the sustainability impact of solvents.[41–43] While precise tools such as GREEN MOTION™ for the perfume and aroma industry and Green Score for cosmetic formulations emphasize the importance of tailored evaluation methodologies for specific industrial applications.[44,45]

As shown in the timeline in Fig. 1, the literature from the past five years demonstrates a clear shift from purely mass-based metrics to multi-criteria, impact- and hazard-aware, sector-specific approaches. Taken together, the taxonomy of mass-based metrics outlined above helps clarify system boundaries and data requirements, thus supporting more consistent benchmarking across methods. In parallel, systems-thinking approaches explicitly link green chemistry to proactive safety orientation, reinforcing the need for metrics that make hazards transparent and actionable.[46] Advances in process-intensification platforms (*i.e.* MAE and UAE) further highlight the importance of quantitative evaluation tools in GE that can compare trade-offs in raw material, time, energy, and chemicals.[3,4] At the industrial/formulation interface, hazard-based multi-endpoint scoring (human health, ecosystem health, and environmental dimensions including sourcing and GHG) demonstrates how quantitative scores can set baselines, prioritize substitutions, and guide innovation, conceptually aligned with SIX Score design choices.[39,45] These directions align with impact-based formalisms coupling mass flows and hazard/impact potentials and with recent multi-criteria analytical metrics, collectively motivating data-efficient yet robust sustainability quantification and software-enabled dissemination.[8,25,38,47]

Currently, GREEN MOTION™ and the more recent Path2Green methodology are, to the best of our knowledge, the only established examples in literature that address GE, highlighting a significant gap in available tools.[44,47] The advancement of multiple methodologies is essential, as relying on metrics developed for different purposes often introduces biases based on individual scientific perspectives, limiting the scope of holistic sustainability evaluations. Moreover, translating green chemistry principles into meaningful and quantitative measures remains a complex challenge, that has yet to be fully addressed. By incorporating diverse data collection, methods, and metric proposals, a more reliable and robust assessment can be achieved. Through the integration of varied approaches and fostering complementary perspectives, the scientific community can move toward a unified goal of enhancing sustainability in GE.

2. SIX Score foundation

As outlined by Nowak *et al.*, the first question to face when a new metric system for green practices is conceived is: What does it mean that "*something is green*"?[48] The definition of green in the field of chemistry was articulated in the twelve principles by Anastas *et al.*,[8] from which were then derived more specific sector such as the Green Analytical Chemistry, Green Engineering, Green Nanomanufacturing, and Green Extraction.[10,34,49,50] Thank to these principles we can manage an idea of greenness, as defined in the main concept "*benign-by-design: design of chemical products and processes that minimize or eliminate the use of generation of substances hazardous to humans, animals, plant and the environment*".[6] This definition, applicable across all sectors of the chemical field, allows greenness to be considered as a state of being. However, it presents challenges in determining the saturation or degree of greenness within a process. Consequently, measurable parameters are essential to compare processes and identify which is "greener". Quantifying greenness in absolute terms is problematic, as any aspect must account for multiple factors that are often impossible to evaluate objectively. All that can be done is to make some arbitrary assumptions, develop a model, and then apply it within the limits imposed by the model itself. In these terms, Nowak *et al.* reported three possible interpretations of the state of being green and sustainable, according to three different linguistic philosophies: purism, pragmatism and formalism (Fig. 2).[48] In developing the SIX Score metric, we chose to adopt the formalism approach. While purism is the most theoretically rigorous, it is largely impractical for real-world application. Conversely, the pragmatic approach is simple and adaptable but offers only relative assessments, which limits standardization and broader comparability. The latter approach is the commonly exploited in metrics closest to GE. Crucially, regardless of the approach adopted, it is essential to explicitly state the methodological basis to ensure transparency and clarify limits and applicability of the evaluation.

The SIX Score approach relies on formalism, which provides a balanced and structured framework, allowing the definition of standardizable reference values while maintaining consistency and repeatability. The benchmark thresholds of the method were defined using both literature data and long-standing practical experience in the field of extraction. The conceptual core of the SIX Score was developed with the six principles of GE as its foundational pillars, as outlined in eqn (2).

$$\text{SIX Score} = f\ (1.\ \text{RM}, 2.\ \text{S\&A}, 3.\ \text{Extr}, 4.\ \text{P\&E}, 5.\ \text{W}, 6.\ \text{P}) \quad (2)$$

Fig. 2 Green chemistry evaluation interpretations: purism, pragmatism, formalism.

where RM: raw materials; S&A: solvents & additives; Extr: extraction; P&E: process & equipment; W: waste and P: product. Each principle is represented as an EF to capture its core concept. To ensure a systematic and comprehensive analysis, each EF has been divided into subcategories, which reflect the specific components contributing to the principle's overarching objective. These subcategories were then incorporated into a mathematical framework, where each component is quantified by assigning the severity of the hazard, multiplied by its associated quantity. This intuitive approach to measure sustainability can be defined by the function reported in eqn (3).

$$\mathrm{EF} = \mathrm{f}\ (h, p, q) \tag{3}$$

where h is the severity of the hazard, which depends on the characteristics of a given factor, q is the quantity of this factor, and p is the effectiveness of counteracting the hazards (prevention).[48] As an intrinsic characteristic of all impact-based metrics, expanding the system boundaries inevitably increases data requirements. To mitigate the potential burden on operators, the protocol is designed to rely mainly on readily accessible inputs and direct physical measurements (*e.g.*, masses, volumes, pressure, energy consumption), complemented by internationally harmonized references (*e.g.*, Globally Harmonized System—GHS classifications), ensuring reliable and sustainability-relevant assessments with manageable data demands. From a practical standpoint, the numerical value adopted for the quantification of the sustainability impact of each EF, has been drawn on widespread and accepted concept of Penalty Points (PPs). This approach was first introduced in 2006 by Van Aken *et al.* through the Eco-Scale analysis applied to organic synthesis and was subsequently extended to related fields for the development of sustainability metrics such as Analytical Eco-Scale, GREEN MOTION™, Green Score, and CHEM21.[28,34] In this framework, the total greenness value starts from a theoretical maximum of 100. PPs are then subtracted based on the degree of hazardousness, h, and the quantities, q, involved in the procedure. Further prevention strategies, p, such as solvent recycling, are also taken into consideration giving a contribution to the final score evaluation. Therefore, the calculation for each EF follows the formula in eqn (4).

$$\mathrm{EF} = 100 - \sum \mathrm{PP}_{\mathrm{subcategory}} \tag{4}$$

where PP are assigned to each EF's subcategory. The final metric value is the average score of the six. EF: raw materials, S&A, extraction, P&E, waste, and product (as for eqn (5)).

$$\mathrm{SIX\ Score} = \frac{\sum \mathrm{EF}}{6} = \frac{\sum \left(100 - \sum \mathrm{PP}_{\mathrm{subcategory}}\right)}{6} \tag{5}$$

The resulting SIX Score provides a single aggregated value for comprehensive comparison of alternative protocols by equally considering all elemental factors without assigning greater weight to any individual component. This overall score offers a balanced perspective on process performance, while the individual elemental factor scores can be examined to identify specific strengths and weaknesses. Such detailed insights facilitate identification of critical points for improvement, informed evaluation of trade-offs between intended enhancements and potential drawbacks. Table 1 reports each EF together with its subcategories, outlining the goal assessment and the evaluation boundaries. These boundaries are defined to clarify the scope of the methodology, which is not intended to replace LCA, but rather to facilitate sustainability evaluation during the early stages of research and process optimization.

Consequently, the methodology does not incorporate systemic parameters, specific market scenarios or geographical contexts, that typically become quantifiable only once a process is implemented at commercial scale, such as energy source and cost, transportation and storage logistics, retail pricing of chemicals and equipment, plant footprint, and infrastructure-related impacts including equipment lifecycle emissions. In addition, the system is limited in addressing specific long-term effects, such as waste bioaccumulation, chronic toxicity, and end-of-life disposal impacts.

A detailed description for each EF, along with specific PP calculation method, is presented in the following chapters. These evaluations are complemented by case studies derived from the author's laboratory experience, providing practical insights into the application of the proposed methodology (SI).[51–55]

Table 1 SIX score elemental factors (EF) definition

Elemental Factor (EF)	Subcategories	Assessment Goals	Evaluation Boundaries
Raw Material	• Feedstock generation • Availability • Seasonality	Promote sustainable resource utilization by minimizing environmental impact and preserving natural resources	The transportation and storage cost related to the matrix
Solvent & Additives	• Hazardousness • Quantity	Reduce hazardous solvent use to safeguard human health and the environment	Lifecycle emissions, long-term impacts and costs
Extraction	• Depletion Efficency • Solvent Impact • Carbon Economy • Time Efficency	Optimize extraction efficiency maximizing yield and carbon valorization while minimizing time and petroleum-based solvents	Considers carbon economy overriding CO_2 sequestration. Bio- *vs.* petroleum-solvent production chains
Process & Equipment	• Pressure • Energy Consumption	Enhance safety and technological efficiency by favoring compact, unpressurized, low-energy apparatus	Energy source and cost, equipment's investment and lifecycle impact and plant footprint
Waste	• PME • Solvent Intensity • Additive Intensity	Minimize waste generation with consideration for the chemical nature and impact of byproducts	Disposal costs and long-term impacts of discarded material
Product	• Selectivity • Contaminants	Ensure high-quality extracts with low toxicity and high concentrations of target molecules	Product lifespan and end-life disposal

3. Elemental factors of SIX Score: an outlook

3.1. Raw material

The use of renewable raw material is the first point addressed by the six principles of green extraction: "*Innovation by selection of varieties and use of renewable plant resources*". Within this framework, biomass selection should prioritize sources with inherent renewability.[56] In summary, the raw material's sustainability was evaluated based on three key factors: (i) feedstock generation, (ii) availability, and (iii) seasonality. Each of these EF's subcategories is assessed, scored, and integrated into a mathematical model, as shown in Fig. 3. This EF aims to minimizing the natural resource deployment, but it does not target the inner cost for storage and transportation of the material as they are restricted to the industrial site location and supply chains.

Feedstock generation. The first criterion for assessing raw material sustainability in biorefineries is the classification of feedstocks into four generations (first, second, third, and fourth), each exhibiting distinct sustainability features.[57] In the following discussion, biomasses are ordered according to a decreasing penalty score, starting from those associated with higher sustainability penalties and progressing toward more favorable cases. Within the feedstock classification, first-generation biomass, derived from food crops cultivated on dedicated agricultural land, is assigned a PPs value of 2. This reflects its low sustainability profile, characterized by direct competition with food production, high demand for land, water, fertilizers, and pesticides, and significant greenhouse gas (GHG) emissions during cultivation.[58] Third-generation feedstocks, primarily algae and microorganisms, are assigned a PPs value of 1. Although they do not compete directly with food crops and can offer high productivity, their cultivation still requires considerable inputs of water, nutrients, and energy, resulting in non-negligible CO_2 emissions.[59]

Fourth-generation feedstocks, including engineered algae, cyanobacteria, and crops, promise higher resource efficiency through molecular engineering but face constraints from technological, regulatory, social, and ecological uncertainties.[60] Second-generation feedstocks, derived from lignocellulosic biomass and agricultural or industrial residues, are not penalized (PPs = 0) as they offer the best overall sustainability performance. These feedstocks do not compete with food crops and are sourced from abundant, non-edible residues often classified as waste, which typically carry negative economic value due to disposal costs.[61]

Availability. The second subcategory considers global resource availability. To promote sustainability, higher scores are assigned to protocols that valorise the world's most abundant crops, which generate large amounts of biomass and waste during processing. Conversely, protocols based on minor crops or wild species are scored lower, reflecting the

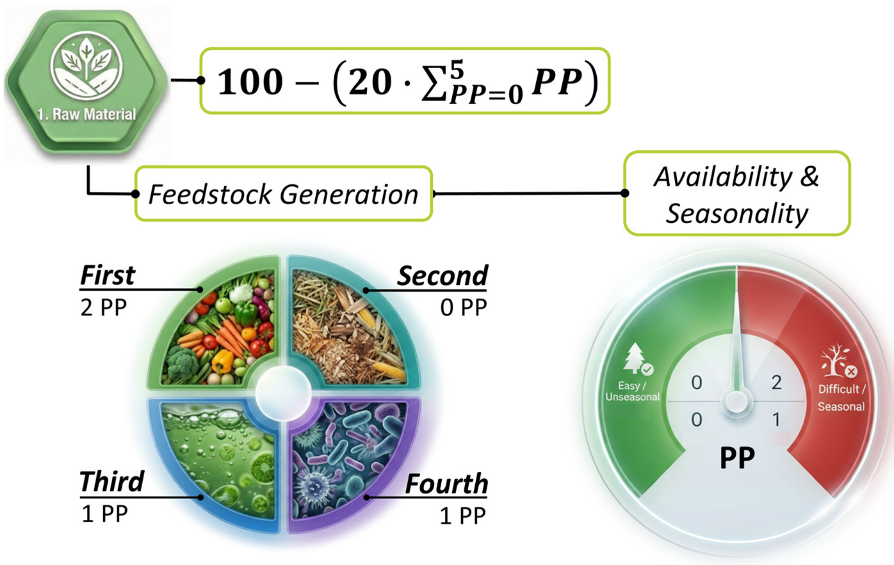

Fig. 3 Raw material EF conceptual representation and calculations. ∑ range spans from 0 to 5, in accordance to the combination extremes: most preferable (0 PP) – feedstock generation: second (0 PP); availability & seasonality: easy (0 PP) + unseasonal (0 PP). Less preferable (5 PP) – feedstock generation: first (2 PP); availability & seasonality: difficult (2 PP) + seasonal (1 PP).

need to preserve biodiversity in line with international agreements such as the Nagoya Protocol and the Convention on Biological Diversity (1992).[62,63]

To determine a threshold distinguishing between high and low global availability, production data from FAOSTAT for the year 2023 were analyzed.[64] The assessment covered 45 items, including both primary crops and biomass feedstocks (Fig. S1). A Pareto analysis of global production quantities was conducted, and feedstocks contributing less than 1% to cumulative global production were classified as low-availability items (Fig. S2). Based on this analysis, a global production threshold of 10 million tons per year was established: feedstocks with annual production below this value were categorized as having relative low availability. In addition, non-food sources, specifically lignocellulosic biomasses (*i.e.* wood waste), were also considered in the estimation. As previously reported, according to a 2018 Eurostat analysis, wood residues account for approximately 24% of total biogenic waste generated in Europe, corresponding to an annual volume of about 48 million tons.[65]

Seasonality. Last subcategory in this EF includes the seasonal availability of resources, which can constrain the consistent supply of raw materials, pose logistical and economic challenges, and potentially disrupt ecological balance.[66] To account for this limitation, species with a harvesting window equal or shorter than one season per year are penalized. To comprehensively address these aspects, the sustainability metric assigns PPs based on availability constraints: 2 points for resources that are globally scarce in quantity, and 1 point for those subjects to seasonal availability.

The total number of PPs assigned to a raw material is first calculated as a sum and then expressed as a percentage of the maximum possible PPs obtainable in this EF. This percentage is subsequently subtracted from 100 to determine the raw material score.

Factors such as transportation are not included in this metric because they depend on the location of the final production plant. The SIX Score focuses exclusively on the process, excluding elements such as transportation logistics, energy sourcing, and operating costs. These aspects are beyond the scope of this metric and are intended to be addressed through a comprehensive LCA once the optimized process is implemented in a real-world market scenario within a geographically designated production facility.

3.2. Solvent & additives

The choice of the optimal extracting medium is a fundamental aspect in calculating the greenness of an extraction procedure. The extracting medium refers to the solvent used to solubilize the target compounds, often in conjunction with functional additives. These additives include chemical agents that serve various functions, such as pH regulation, metabolite stabilization, and textural modification, or biological agents such as enzymes. The extracting medium constitutes a large proportion of the total mass in the procedure, with the solid-to-liquid ratio reaching even up to 1 : 50/1 : 100.[67,68] Ideally, solvent-free extraction methods offer the most sustainable approach; however, technological barriers make these methods uncommon. When solvents are necessary, water is the most sustainable option due to its high availability, low cost, non-toxic nature, and minimal equipment requirements.[69] However, water is limited by its high polarity, which restricts its ability to extract non-polar compounds. This limitation can be overcome by modulating pressure and temperature, allowing water to transition into subcritical or supercritical states. In these conditions, water's polarity decreases, enabling the extraction of a broader range of compounds, including less polar and even apolar substances.[70] Additionally, the extraction efficiency can be further enhanced using additives. Surfactants can be introduced to improve the recovery of apolar compounds by reducing surface tension and enhancing solubilization.[71] Cyclodextrins can be employed to entrap specific molecules, acting as host molecules for a wide variety of compounds, while chelating agents may be added to selectively remove metals from the matrix.[72,73]

However, the introduction of such additives must be carefully evaluated, as their sustainability depends on their chemical nature, biodegradability, toxicity, and quantities used. By balancing the choice and concentration of additives, it is possible to enhance the versatility of the extraction medium while maintaining a sustainable process, ensuring that the benefits for GE are not offset by the environmental impact of auxiliary chemicals. Furthermore, Generally Recognized As Safe (GRAS) solvents, as defined by FDA legislation, are viable options. However, despite their safety designation, GRAS solvents can still present sustainability challenges, such as vapor emissions and flammability, which must be factored into their evaluation. In parallel, several unconventional solvents are arising for the extraction of biomass such as supercritical fluids, ionic liquids, deep eutectic solvents, and supramolecular solvents providing sustainable alternatives to traditional organic solvents. To guide solvent selection, frameworks such as CHEM21 and REACH provide valuable principles for assessing the safety, health, and environmental impacts of chemicals. CHEM21 categorizes solvents based on their safety and environmental impact, incorporating GHS criteria.[42] The REACH framework ensures chemicals meet strict regulatory standards for human and environmental safety.[74] It is worth noting that the goal of this EF is to minimize the use of chemicals by favoring those with less hazardous nature, but its evaluation boundary does not target costs related to solvents or additives (*i.e.* purchase, storage, transportation).

Hazardousness and quantity. Building on the foundational principles of CHEM21 and REACH, we developed a simplified evaluation metric tailored to the specific needs of extraction processes (Fig. 4). SIX Score incorporates GHS-based hazardousness assessments, assigning PP for hazard pictograms and warning labels such as "Warning" or "Danger" together with the gas emissions during processing for consider a further occupational hazard.[75] Concerning pressurized fluids (*i.e.* subcritical water and supercritical CO_2), those systems do not account for the related GHS pictogram ("compressed gas"), as the system pressure feature is already included into the process & equipment EF. These elements define the hazar-

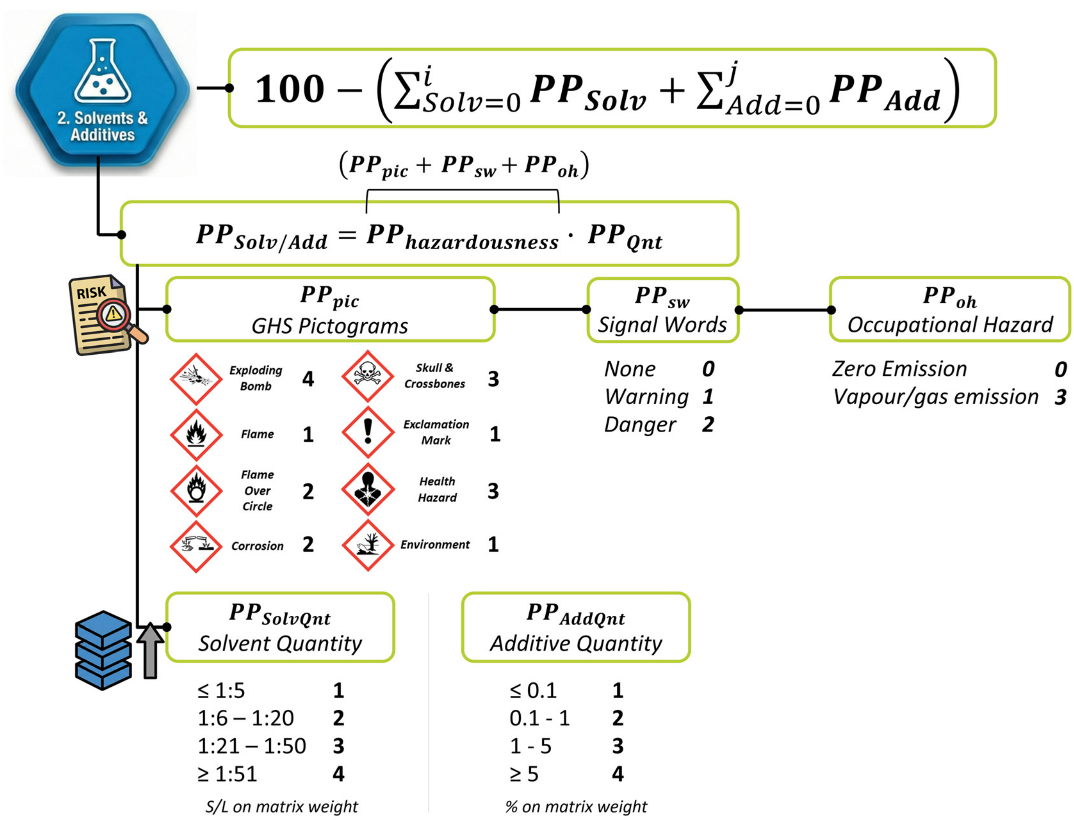

Fig. 4 Solvent & additives EF conceptual representation and calculations. PP solvents (PP_{solv}); PP additives (PP_{add}); PP pictograms (PP_{pic}); PP signal words (PP_{sw}); PP occupational hazards (PP_{oh}), PP solvent quantity ($PP_{solvqnt}$); PP additive quantity (PP_{addqnt}).

dousness of the substance, which is then scaled based on the quantity, normalized to the processed biomass. This approach, similar to the Environmental Quotient (EQ) or the ChlorTox Scale, provides a comprehensive assessment of chemical risk by considering both the substance's inherent hazardousness and its actual quantity.[76,77]

If the user is uncertain about the selection of alternative solvents, COSMO-RS can be coupled with the SIX Score to support solvent selection: COSMO-RS enables the computational screening of candidates consistent with process chemical requirements, while the SIX Score provides a subsequent evaluation of their sustainability and performance.[78] To extend the scope beyond solvents, our approach applies the same framework to additives, ensuring a comprehensive evaluation of all chemical components involved in the extraction media. In this framework, every chemical used for the extraction, from common solvents to complex mixture (such as the deep eutectic solvents), can be evaluated based on its hazardousness and relative amount with respect to the extracted biomass. The two calculations for solvent and additives are separated and the accumulated PP are subtracted to the final score for the solvent & additives EF. Because, as mentioned, the definition of a "green solvent" (and, more broadly, a "green extracting medium") is inherently multifactorial, and ecotoxicological outcomes can vary substantially depending on the endpoints, SIX Score adopts a transparent, reproducible evaluation logic grounded on information that is broadly available to users, (*i.e.*, GHS dataset retrieved from safety data sheets, SDS), combined with the solvent and additive amounts normalized to processed biomass. To illustrate how this framework can support practical screening of extraction media, in the SI it includes a review of a wide range of extraction scenarios (Tables S1A–L, G, S3A, B and Fig. S3). Solvent & additives EF changes when switching across solvents and additives ranging from water/ethanol to conventional organics (such as acetone, hexane, chloroform), deep eutectic solvents and selected emerging alternatives (such as CPME, 2-MeTHF, Cyrene). The tabulated example highlights that changes in solvent/additive identity and dosages primarily affect the solvent & additives EF (*via* hazard and quantity), whereas equipment- and performance-related inputs (*e.g.*, energy, pressure, yield/selectivity) remain procedure-specific and must be supplied from experimental data to obtain a complete SIX Score assessment.

While this approach offers an accessible tool for optimizing extraction medium sustainability, it does not encompass broader elements such as environmental impact associated to chemicals manufacturing and disposal. In this term, a partial consideration depending on the origin of solvent, dividing in bio- and petrol-derived, is introduced in the EF extraction in section "3.3 Extraction". Additional tools such as VEGA and EcoSolvent® could also be integrated to further extend the evaluation, combining *in silico* predictions of toxicological and ecotoxicological properties with an LCA-based analysis of solvent-related environmental impacts.[41,79]

3.3. Extraction

The EF Extraction encloses all the variables related to the efficiency of an extraction process divided into four subcategories: (i) matrix depletion efficiency, (ii) solvent impact, (iii) carbon economy and (iv) time effectiveness (Fig. 5). Each subcategory is assigned a maximum of 25 PPs, and the cumulative PPs are subtracted from 100 to yield the final Extraction score. PP values from 0 to 25 for all four subcategories were calculated using a regression curve, obtained by interpolating subcategory data with the PP to derive the interpolation equations (Fig. S4–S7).[80]

Matrix depletion efficiency. This subcategory measures the amount of the target compound (or class of compounds) extracted relative to their concentration in the matrix. This parameter can be determined using a conventional extraction method (as recognised in standard literature, for example, the *Pharmacopoeia*) or by exhaustive sequential extraction to establish the maximum depletion. It should be noted that the depletion efficiency is strongly dependent on the imposed target.

Solvent impact. It considers the number of solvents used in the extraction and their renewability, whether they are petrol-based or bio-derived. This criterion aims to recognise protocols that use bio-derived solvents. Indeed, a variety of solvents, such as methanol, ethanol, 1-butanol, ethyl acetate, can be either petrol-based or bio-derived.[81] A special issue of Catalysis Today, "*Sustainability Metrics of Chemicals from Biomass*", in 2015 demonstrated with a designed sustainability metric, cradle-to-gate comparison, the clear environmental advantage of renewable biomass-based chemicals over fossil-based alternatives.[82] Furthermore, new sustainable metrics for biomass-based carbon chemicals were defined underscoring the critical role that the production source of chemicals plays in overall sustainability.[83] It should be noted that this subcategory does not take in charge the costs of the different solvent sources.

Carbon economy. Another important factor in assessing the efficiency of biomass conversion into the final product is the choice of metric. AE was discarded for this application due to the difficulty of determining the precise atomic composition of natural biomass, while carbon economy (CE) provides a more practical metric.[84] In the actual calculation, rather than directly quantifying the number of carbon atoms, the amount of organic fractions was used as a proxy. These organic fractions can be related back to the same conceptual equation for CE but were experimentally obtained through mineralization/calcination protocols applied to both the initial biomass matrix and the final product (eqn (6)).

$$\mathrm{CE} = \frac{\left[\mathrm{tot\,yield}\left(\dfrac{g\,\mathrm{extr.}}{g\,\mathrm{matrix}}\right)\cdot \mathrm{extr.\ org.\ fract.}\left(\dfrac{g\,\mathrm{org.\ fract.}}{g\,\mathrm{extr.}}\right)\right]}{\mathrm{matrix\,org.\,fract.}\left(\dfrac{g\,\mathrm{org.\ fract.}}{g\,\mathrm{matrix}}\right)} \tag{6}$$

Accordingly, the carbon fixation is put in relation with the recovered organic fraction, not directly with the CO_2. If exter-

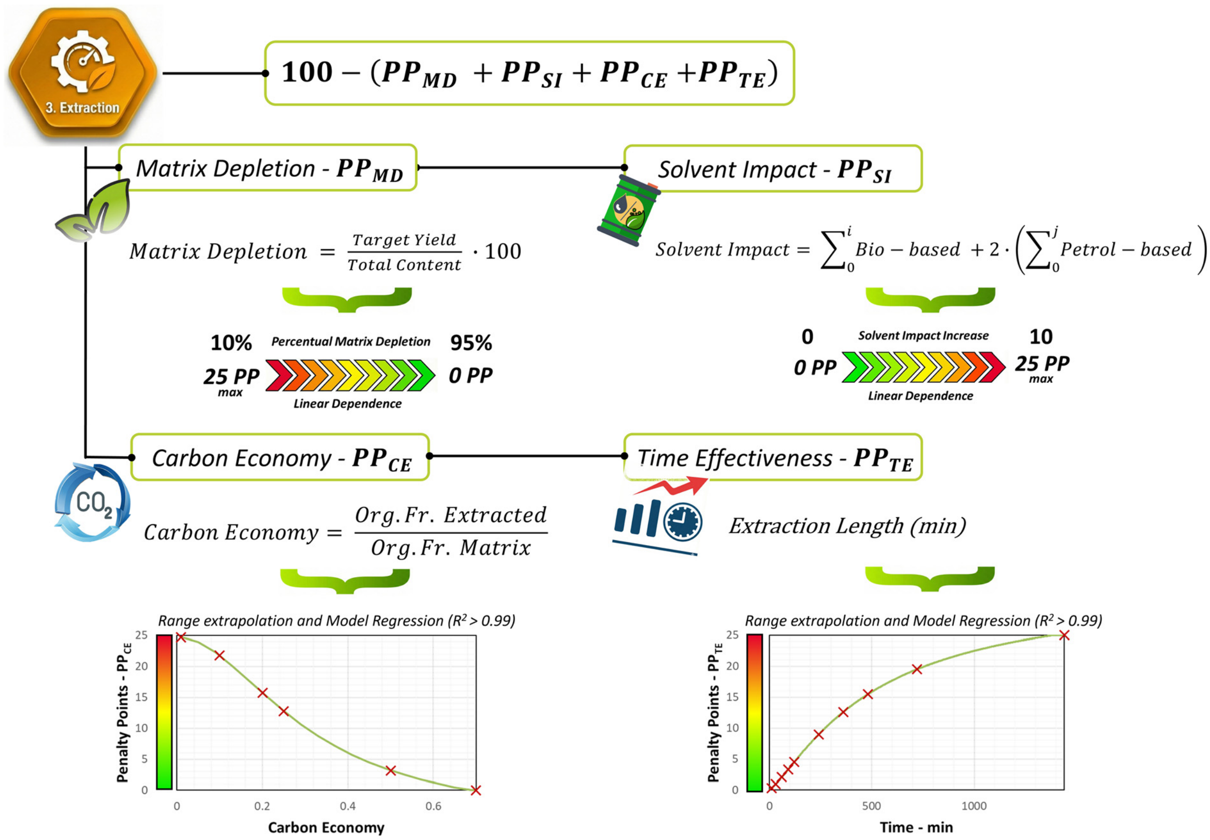

Fig. 5 Extraction EF conceptual representation and calculations. PP matrix depletion (PP_{MD}); PP solvent impact (PP_{SI}); PP carbon economy (PP_{CE}); PP time effectiveness (PP_{TE}). organic fraction (org. fr.).

nal inorganic materials (*e.g.*, buffering salts) are used during the process, their contribution should not be accounted, so that the mass balance for the extract reflects only constituents originating from the initial biomass. Efforts to improve this parameter will promote more efficient use of raw material, reduce waste generation and, consequently, lower CO_2 emissions associated with waste disposal.[85]

Time effectiveness. This subcategory refers to the duration of the process. In the case of a batch process, is considered the time necessary to complete the extraction process, including heating ramp and cooling, but excluding any pre-treatment and downstream procedures, which are considered in the fourth EF "*Process & Equipment*". For sequential procedures, the cumulative time of the separate extraction steps is considered, when the cumulative yield is reported. For continuous-flow processes, this parameter can be expressed as the residence time of the biomass within the reactor, calculated as the ratio of the extraction chamber volume to the solution flow rate, multiplied by the total number of passes. This formulation enables an objective evaluation of flow-based extraction systems in terms of process efficiency. Consequently, low-flow or long-residence-time processes, which are typically less efficient, are appropriately penalized within the assessment framework.

3.4. Process & equipment

The implementation of a process concept requires appropriately designed and dimensioned equipment, as process feasibility fundamentally depends on the availability of a well-defined, physically achievable, and scalable configuration (Fig. 6).

The sustainability of the final set-up can be pursued by following the six principles of GE and the twelve principles of green engineering.[7,42] These principles advocate for the design of materials, products, processes, and systems that are inherently non-hazardous, prioritize waste prevention over treatment, and optimize efficiency in terms of mass, energy, space, and time. The biomass extraction process typically involves multiple unit operations, such as drying, shredding, extraction itself, solvent separation and purification. While each step contributes to the effectiveness of the protocol, it also increases the requirements for time, energy, and space. The main challenge is to reduce the number of steps by designing more compact and integrated processing units. As highlighted in previous research, design optimization will play a role in the hybridization of unit operations, ideally shifting from sequential to simultaneous treatments within a single hybrid reactor.[86] This approach considers the synergies and trade-offs

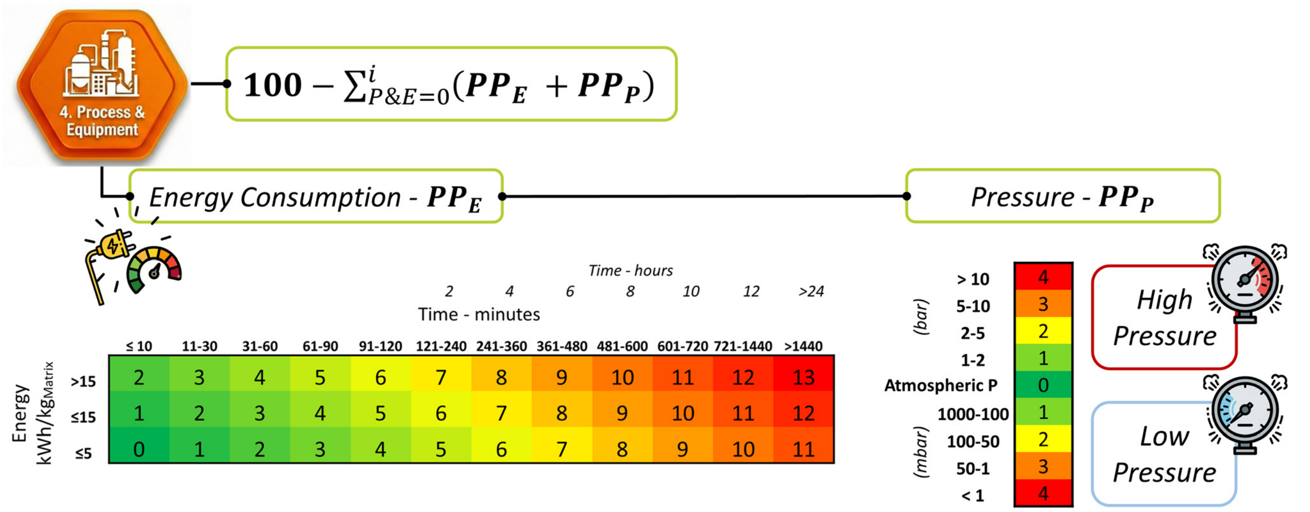

Fig. 6 Process & equipment (P&E) EF conceptual representation and calculations. PP energy consumption (PP_E); PP pressure (PP_P).

inherent to such integration, aiming to enhance efficiency while addressing potential challenges. As emphasized by the Gestalt principle, "*the whole is different from the sum of its parts*", the hybridization of two technologies creates a new system that is distinct from, but not necessarily superior to, the individual technologies. Potential drawbacks include increased time and energy consumption or inherent incompatibility between the two technologies when combined.

This highlights the importance of carefully evaluating extraction systems to ensure they achieve genuine synergy rather than introducing inefficiencies or mismatches. In the proposed metric for evaluating equipment efficiency, we consider both the hazardousness and relative cost associated with the equipment, expressed in terms of pressure requirements and overall energy consumption. As a related boundary, this EF does not account for equipment lifecycle and investment, energy cost and origin, as well as plant footprint.

Energy consumption. The subcategory accounts for the energy required to process a defined amount of biomass, expressed as kWh k_{matrix}^{-1}. In this framework, energy consumption is normalized to the amount of biomass processed, reducing scale-related bias and enabling a more accurate comparison across extraction systems, particularly regarding industrial relevance. Because energy demand is inherently coupled to extraction temperature, temperature is not considered an independent parameter; instead, its influence is implicitly included in the overall energy consumption. Data on energy requirements and total biomass throughput for different extraction technologies were compiled, and median values were subsequently employed to define sustainability benchmark thresholds, as detailed: high > 15 kWh kg_{matrix}^{-1}, medium $5 \le x \le 15$ kWh kg_{matrix}^{-1} and low < 5 kWh kg_{matrix}^{-1} (Fig. S8). These values are then put in relation with the specific operating time of each piece of equipment within the procedure, by the creation of a matrix, as reported in Fig. 6.

Pressure. Systems that handle high-pressure or vacuum need specialized equipment, increasing production costs and risks for operators. The proposed pressure intake scale ranges from less than 1 mbar to more than 10 bar with the greenest score attributed to non-pressurized system.

The shift from batch to continuous processes in chemistry and GE is widely recognized for enhancing efficiency and scalability.[87–89] However, continuous-flow systems are not inherently more sustainable than batch systems. Poorly designed set-ups can result in reduced flow rates, limited production, poor mass transfer, and increased energy consumption. Rather than assigning additional sustainability points to continuous systems *a priori*, their advantages are already reflected in the metric, such as reduced extraction time under the EF Extraction and an evaluation of energy consumption in the EF process & equipment. This approach ensures a balanced assessment of the sustainability potential of flow systems. Further evaluations associated with the energy source and plant investment cost are omitted since those factors are related to subjective case scenario that are not assessable during protocol optimization and, as mentioned, belong to LCA features.

3.5. Waste

The shift from an "end-to-pipe" approach, focused on disposal procedure efficiency, to the zero-waste approach has played a critical role in the development of innovative processes. However, in extraction protocols the waste is an intrinsic factor that cannot be completely removed, at least without considering conversion procedures addressing the structural part of biomasses (Fig. 7).

Indeed, if extraction is viewed as the separation of molecules from a matrix, the residual part, not targeted by the extraction, is considered waste or, at best, a by-product. Furthermore, the use of solvents, including water and addi-

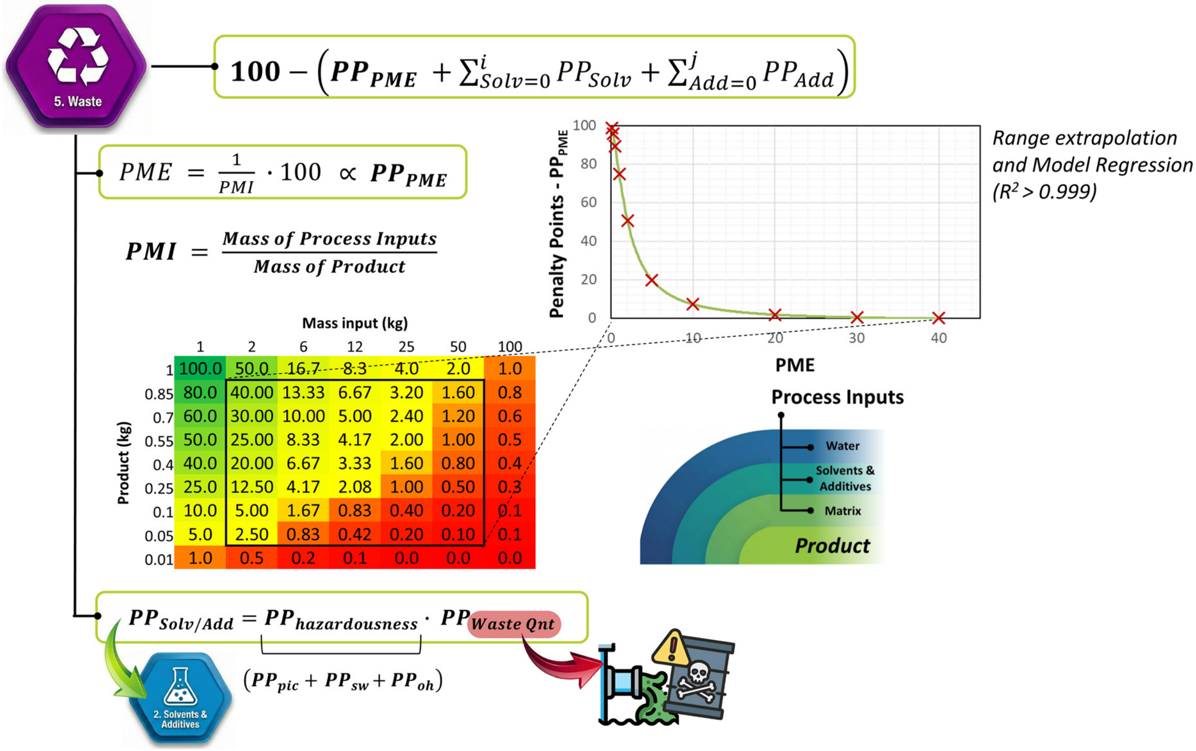

Fig. 7 Waste EF conceptual representation and calculations.

tives, are also equalized as waste material when not recovered/recycled. Starting from this concept, the fourth principle of GE "*production of co-products instead of waste towards bio-refinery concepts*" defines a new strategy to deal with. The proposed metric in relation to this aspect aims to calculate waste production, giving also an evaluation of their nature, by penalizing the generation of toxic residues. Importantly, any solvents or biomass that are recycled and reused within the protocol are considered co-products rather than waste and are therefore excluded from the calculated waste quantity. One of the best-known parameters for waste calculation in chemistry is the *E*-factor, which even after 30 years, is still giving an uncountable contribution to underlining the problem of waste production (and to its prevention) across many fields, especially in the pharmaceutical and fine chemicals industries.[90] However, this milestone metric typically does not include water and the hazardous level of waste. The rationale to exclude water was based on its potential to distort *E*-factor values in chemical processes, due to the high quantity used, and the fact that water usage typically does not have a significant environmental impact in comparison to hard-chemicals. Anyway, given the current global water crisis and water's role as the primary solvent in green extraction, it is crucial to minimize the wastage of this invaluable resource. In this term, another metric was adopted for the calculation of the sustainability impact of waste in SIX Score, PMI.[18] Introduced by the EPA and ACS GCI in 2006, PMI has been chosen because water is included in the calculation.

Its derivatization in percentage expression gave easy-to-read results known as Product Mass Efficiency (PME), which was ultimately applied in this metric. Even in this case, however, the quality, or safety, of waste production is not considered. In consideration of this point it is not fair to give the same level of environmental impact on the production of a kg of water as waste or a kg of petrol-based solvent. The father of the *E*-factor, Roger Arthur Sheldon, has already considered this aspect and proposed the EQ as a solution.[76] This mathematical approach involves multiplying the *E*-factor by an unfriendliness quotient (Q), assigned based on the toxicity of the waste, to provide a weighted assessment of environmental impact. To address these considerations, the waste parameter calculation has been designed by diving it into 3 sub-categories: (i) PME, (ii) solvent intensity, and (iii) additive intensity (Fig. 7). Total PME serves as the primary basis for evaluating overall material efficiency within the process.

The calculation of this subcategory starts with the PME of the extraction, which is then used to extrapolate a corresponding PP_{PME} exploiting an appropriate calibration curve. The rationale behind the curve's design was to reflect realistic expectations. Given that extraction inherently involves separating specific molecules from biomass, achieving a PME value of 1, ideally a 100% level of sustainability, is not concretely feasible. Moreover, giving the relatively low concentration of extractable components in feedstocks, which are predominantly composed of structural molecules, such as cellulose, hemicellulose and lignin, the extraction yield of these compounds typically represents only a small fraction of the total biomass weight. To describe possible scenarios, a matrix grid has been developed, correlating PME output on a normalized amount of biomass of 1 kg, varying the extraction yield in relation to solvent/mixture ratio. This grid allowed the identification of upper and lower threshold values, which were used to define realistic efficiency boundaries for converting raw biomasses into extractable products. These thresholds were set at PME values of 40 and 0.16, corresponding to PP_{PME} scores of 0 and 99, respectively. The resulting regression exhibited a hyperbolic (sigmoidal) trend, with the highest sensitivity deliberately designed to occur within the PME range of 10 to 0.5, resulting in the equation presented in Fig. S9.[80] Values beyond this range only marginally adjust the penalty score, as they already reflect extreme and less realistic process conditions. As a result, extraction processes that are highly efficient and use matrices inherently rich in the target compound achieve higher sustainability scores, due to reduced waste generation. This feature encourages the full exploitation of feedstocks (*i.e.* sequential extraction), and also the initial selection of matrices rich in extractables. Additionally, solvent PME and additives PME add SI PPs based on the nature of the solvent or additive discarded, following the penalty criteria outlined in the solvents & additives section. However, those penalties are re-adjusted according to the final amount discarded. This strategy serves a dual purpose: first, to enable a qualitative assessment of waste generation; and second, to allow the application of the prevention parameter (p), as previously outlined in eqn (3). The resulting metric is designed to recognize and reward recovery strategies that reduce hazardous impacts, particularly where appropriate management of toxic chemicals is implemented. As a related boundary, this EF does not account for disposal costs or long-term impacts of discarded material.

3.6. Product

The last EF of the proposed metric assesses the quality of the extract obtained from the extraction process, accounting for two subcategories: (i) selectivity and (ii) contaminants (Fig. 8). The imposed boundary is related to end-of-life, peculiar of LCA, where aspects such as material disposal and biodegradability are evaluated.

Selectivity. The first subcategory considered the recovery efficacy for the target compound(s), where higher purity corresponds to a higher green score. PPs for selectivity were assigned based on realistic empirical data, using a scale ranging from 10 mg of target compound per gram of extract (low selectivity) to 500 mg g^{-1} (high selectivity). As with the other regression models, the curve was designed with maximum sensitivity in the 20–300 mg g^{-1} range, where changes in selectivity have the greatest impact on the score (Fig. S10).[80] To maximize this parameter, the extraction should be optimized toward the

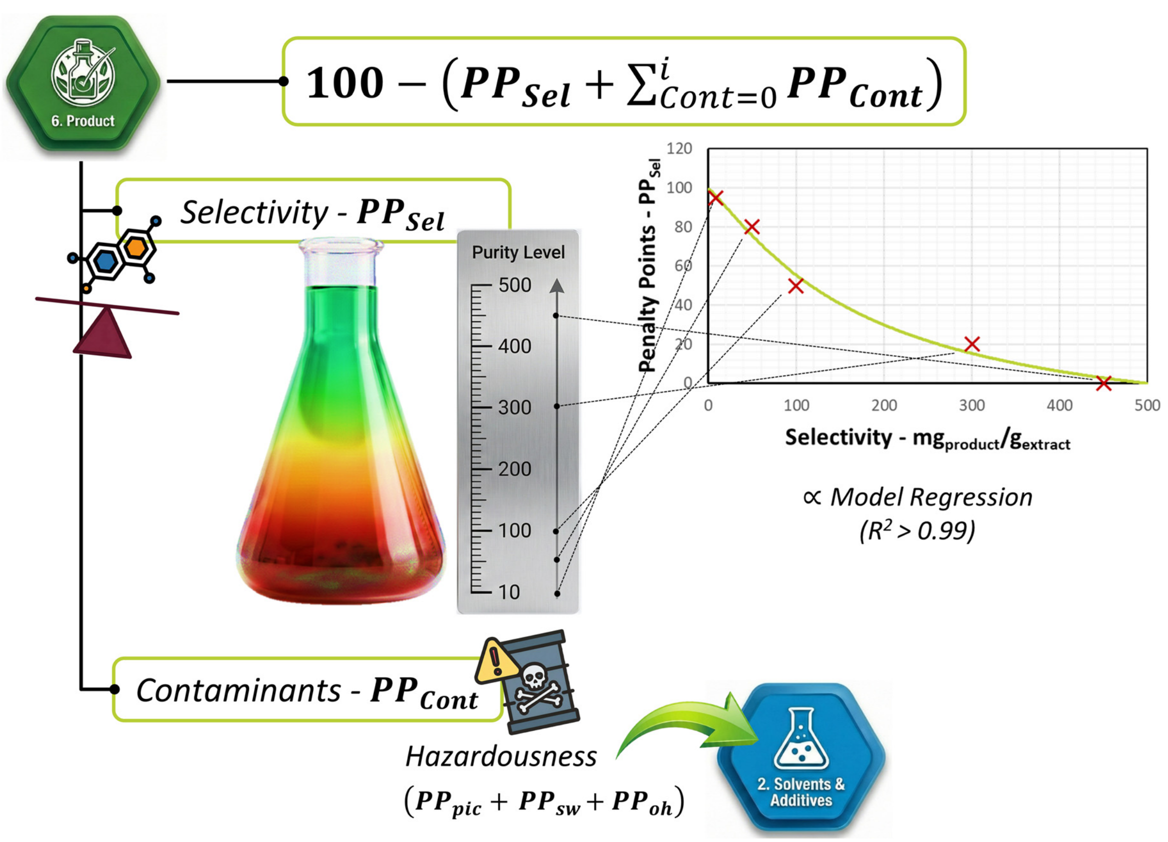

Fig. 8 Product EF conceptual representation and calculations. PP selectivity (PP_{sel}); PP contaminants (PP_{cont}).

target metabolite while minimizing the use of excipients in the final formulation (*i.e.* maltodextrin). It worth notice that purification steps made on low-selectivity extracts can enhance this subcategory, but potentially detrimental to, as example, solvent & additives, process & equipment end/or Waste EFs. In this context, pharmaceutical ingredients typically require higher purity and therefore greater resource inputs than bulk materials such as pectin and alginates.

Nevertheless, the sensitivity range remains applicable within sectors, as the metric is intended for process optimization to identify bottlenecks and improve sustainability, independently from market value.

Contaminants. The second subcategory addresses the presence of exogenous components in the final product, including residual reagents (*e.g.* sodium hydroxide), organic solvents, surfactants, and processing additives. These contaminants not only lower the effective concentration of the target compound but may also raise safety and regulatory concerns, which have been taken into consideration for additional penalties. The corresponding PP, for this subcategory, were assigned according to the criteria described in the solvents & additives section. The final quality score was then obtained by subtracting the cumulative PP associated with the two subcategories: selectivity and contaminants.

4. Software & database

The digitalization phenomenon is spreading across all the industrial sectors in the global economy and is recognized as the fourth industrial revolution, opening a new pathway for sustainability. This scenario highlights the urgency to develop dedicated tools not only for productivity but also for green and sustainable evaluations.[91] To fulfil this need, an open-access web platform has been developed to enhance the exploitability of the proposed metric (SIX Score Hub v.1.0).† The platform provides a user-friendly interface to assess sustainability by guiding users through its six designed EF and subcategories, with explanations for each input (Fig. 9, SI case studies in Fig. S11–S18). As determined by the purism approach adopted in calculating greenness, we believe that this tool requires continuous improvement, which is why we have provided a feature in the software to collect scientists' comments and to support growth with a User-Centered Design approach (UCD). Contributions to the dataset are accepted only when a Digital Object Identifier (DOI) for the associated publication is provided, ensuring that only peer-reviewed studies are incorporated and thereby maintaining the scientific reliability of the database. To ensure transparency and long-term robustness, the SIX Score Hub is designed as a versioned tool in which benchmark assumptions and threshold values (*i.e.* raw-material availability cut-off) are treated as updatable parameters rather than fixed constants. As global production volumes, supply chains, and sustainability standards evolve, thresholds will be periodically revised using updated external datasets and trend information emerging from the platform database, so that benchmarks remain aligned with the most recent evidence.

Operationally, this evolution will follow a structured maintenance workflow that combines routine platform maintenance with periodic benchmark refinement and transparent documentation.

(i) **Monitoring and updating external datasets**: external reference datasets will be monitored and updated consistently

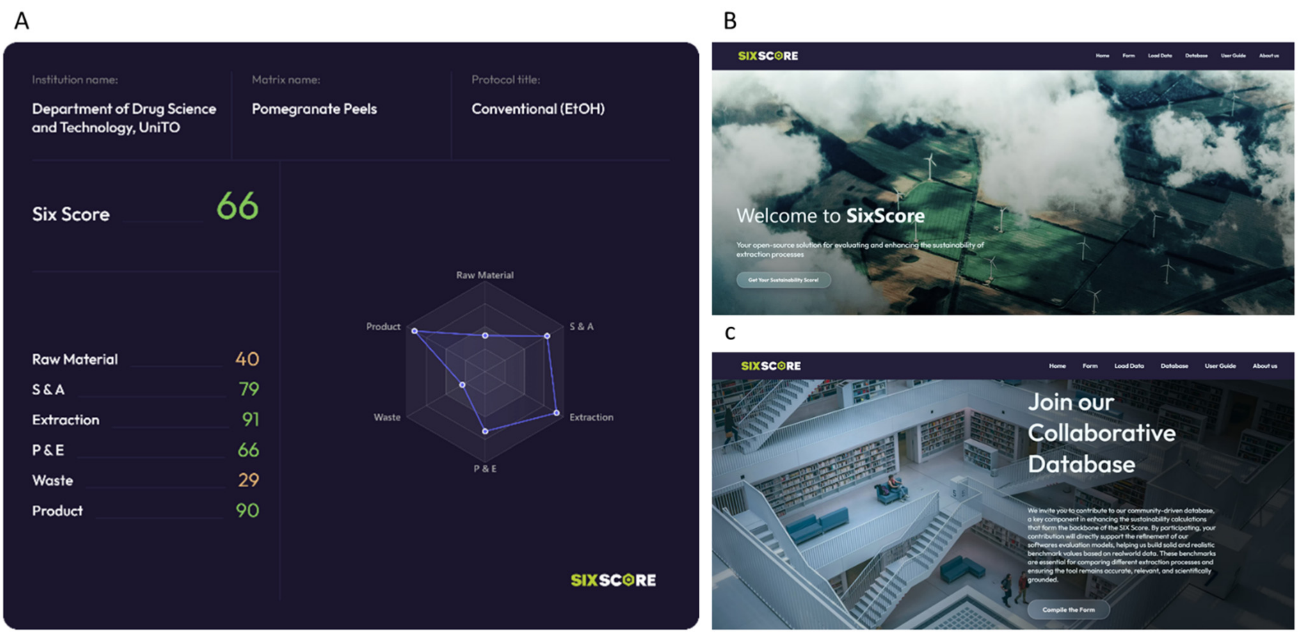

Fig. 9 SIX Score Hub v.1.0 visuals: A: metric final output (see pomegranate peels extraction discussion in SI); B: landing homepage; C: collaborative database.

(authoritative organizations for global production, availability and supply scenario statistics, *e.g.* FAOSTAT). At the same time, continuous screening of literature, particularly reviews, curated databases and repositories, will progressively strengthen the evidence base supporting the benchmark section.

(ii) **Database-driven refinement using Hub's trends**: the Hub's consensual data collection will enable aggregation of population-level trends supporting iterative refinement of thresholds and, where justified, the introduction of updated scoring relationships (*i.e.* non-linear penalty functions), that better capture the evolving state-of-the-art in a rapidly developing field. In this context, the Hub is also conceived as a foundation for implementing machine learning and deep learning workflows (with explicit preservation of traceability), aimed at identifying emerging clusters, proposing data-driven benchmark candidates and supporting scenario-aware decision assistance.

(iii) **Routine Platform maintenance and design evolution**: the platform will undergo annual minor releases, including updates to the user guide and a public changelog, as well as with bug fixes, patches and User Interface/User Experience (UI/UX) improvements guided by a UCD approach. Accordingly, users are asked to report the Hub's release version used for each assessment, to ensure traceability and comparability.

A consolidated methodological update is planned within five years of the system's launch to reflect validated improvements and the maturation of the underlying database.

The data collection and their assemblage in Big Open Linked Data (BOLD) structure is the first step to move for the creation of chemical data intelligence for sustainable chemistry.[92] The collection and integration of diverse data sources are crucial for informed decision-making in GE sustainability.[93] By organizing and analyzing this data effectively, it becomes possible to gain a clearer understanding of the state-of-the-art in extraction technologies and identify areas for improvement, as well as a continuous refining of the adopted ranges for EFs evaluation. The use of artificial intelligence models is recognized as a promising perspective applicable also in the field of metabolite extraction. The main challenges are managing the complexity of plant matrix structures alongside large and complex datasets, ensuring accurate pre-processing and analysis, and achieving scalability for real-time monitoring and process optimization.[94,95]

Looking ahead, advancements in data practices, such as those envisioned in Tim Berners-Lee's 5-star plan for data formats, could further enhance accessibility and structure, paving the way toward a semantic web where data is more context-rich and actionable.[96] Further perspectives, a neural network can analyse this semantic model to predict the environmental impact of a new extraction method or optimize existing processes by suggesting alternatives.[97,98] Data collection and processing thus remain central to the development of future technologies. A centralized platform that aggregates green extraction protocols and new trends will empower scientists and companies to make informed decisions. The perspective both facilitates smart decision-making by enabling comparisons with state-of-the-art technologies and lays the groundwork for the potential integration of semantic web technologies and neural network systems. Together, these advancements could drive the progression of green extraction technologies within the Industry 4.0 framework, fostering a more sustainable and innovative future.

5. Conclusion

The term "green" has become ubiquitous, applied to almost every new initiative or technology. However, not everything can truly be "green", and this terminology relies on an implicit comparison with its opposite, just as there is no black without white. On the other hand, reality is full of shades that must be grasped, and achieving a complete green transition cannot occur overnight. This complexity underscores the need for innovative metrics to define and standardize what qualifies as green. A holistic perspective is crucial for a comprehensive sustainability analysis, but sector-specific evaluations are equally important to meet the unique needs of different industries. To address these needs in the sector of natural compounds extraction, we proposed SIX Score, an open-source methodology and software for assessing and comparing emerging processes within the sustainability framework. While LCAs provide a broader perspective, their complexity and cost make simpler methods more appropriate during early development stages. The SIX Score can be applied at these initial phases, helping to avoid significant errors from the outset while offering targeted guidance for informed decision-making. This approach is also designed to evolve alongside advancements in database analysis through the developed software, ensuring that its framework remains aligned with the latest developments in the green transition and sustainability sectors. In conclusion, we are confident that this new methodology can establish itself within the modern landscape of green extraction, offering a pragmatic contribution to the future sustainable development of this continuously evolving field.

Author contributions

G. Capaldi: investigation, writing (original draft), data curation, formal analysis, co-conceptualization. C. Aimone: writing (original draft), data curation, visualization. G. Mongardi: software, formal analysis, visualization. E. Calcio Gaudino: validation, formal analysis, writing (review & editing). G. Grillo: conceptualization, methodology, writing (review & editing), supervision. G. Cravotto: validation, writing (review & editing), project administration.

Conflicts of interest

The authors declare no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data availability

The authors declare that data supporting this article are available within the article and in the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d5gc07041d.

The latter provides also a Table of abbreviations. References cited in the SI are listed in the main manuscript's reference list, according to the original numbering.

Acknowledgements

Authors acknowledge Ms. Roberta Carrer (Logo design) and Mr Andrea Anchora (Website) for the precious technical support during the graphical development of the SIX Score Hub v.1.0.

References

1 F. Chemat, M. Abert Vian, A.-S. Fabiano-Tixier, M. Nutrizio, A. Režek Jambrak, P. E. S. Munekata, J. M. Lorenzo, F. J. Barba, A. Binello and G. Cravotto, *Green Chem.*, 2020, **22**, 2325–2353.
2 F. Chemat, N. Rombaut, A. G. Sicaire, A. Meullemiestre, A.-S. Fabiano-Tixier and M. Abert-Vian, *Ultrason. Sonochem.*, 2017, **34**, 540–560.
3 M. Melikoglu, *Sustainable Chem. Clim. Act.*, 2025, **7**, 100122.
4 T. Chatzimitakos, V. Athanasiadis, D. Kalompatsios, M. Mantiniotou, E. Bozinou and S. Lalas, *Biomass*, 2023, **3**, 367–401.
5 V. Hessel, S. Mukherjee, S. Mitra, A. Goswami, N. N. Tran, F. Ferlin, L. Vaccaro, F. Malekpour Galogahi, N.-T. Nguyen and M. Escribà-Gelonch, *Green Chem.*, 2024, **26**, 9503–9528.
6 G.-H. Lu and N. Li, Recent progress in sustainable biomass valorization via chemoenzymatic catalysis, *Green Chem.*, 2026, DOI: 10.1039/D6GC00142D. Advance Article.
7 P. Janicka, J. Płotka-Wasylka, N. Jatkowska, A. Chabowska, M. Y. Fares, V. Andruch, M. Kaykhaii and J. Gębicki, *Curr. Opin. Green Sustainable Chem.*, 2022, **37**, 100670.
8 P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, 2000.
9 B. H. Lipshutz and S. Handa, *Green Chem.*, 2026, **28**, 5606–5612.
10 F. Chemat, M. A. Vian and G. Cravotto, *Int. J. Mol. Sci.*, 2012, **13**, 8615–8627.
11 M. Liu, G. Zhu and Y. Tian, *Green Carbon*, 2024, **2**, 425–437.
12 C. Jiménez-González and M. R. Overcash, *Green Chem.*, 2014, **16**, 3392–3400.
13 I. Niiranen, S. Forssell, P. Oinas and R. Dickson, Techno-economic and life cycle assessment of tannin production from spruce bark for leather industry applications, *Green Chem.*, 2026. DOI: 10.1039/D6GC00120C. Advance Article.
14 E. Lucas, A. J. Martín, S. Mitchell, A. Nabera, L. F. Santos, J. Pérez-Ramírez and G. Guillén-Gosálbez, *Green Chem.*, 2024, **26**, 9300–9309.
15 B. M. Trost, *Science*, 1991, **254**, 1471–1477.
16 R. A. Sheldon, *Chem. Ind.*, 1992, **23**, 903–906.
17 C. Hu, C. J. Testa, S. C. Born, W. Wu, K. Shvedova, R. Sayin, B. S. Halkude, F. Casati, A. Ramnath, P. Hermant, B. Takizawa, T. F. O'Connor, X. Yang, S. Ramanujam and S. Mascia, *Green Chem.*, 2020, **22**, 4350–4356.
18 S. Eichwald, H. Ostovari, H. Minten, J. Meyer-Waßewitz, D. Förtsch and N. von der Assen, *Green Chem.*, 2025, **27**, 10153–10168.
19 J. R. Silverman, *J. Chem. Educ.*, 2021, **98**, 2741–2745.
20 A. D. Curzons, D. J. C. Constable, D. N. Mortimer and V. L. Cunningham, *Green Chem.*, 2001, **3**, 1–6.
21 A. M. Afanasenko, N. Deak, J. October, R. Sole and K. Barta, *Green Chem.*, 2025, **27**, 5947–5981.
22 A. Bardow, J. Pérez-Ramírez, S. Sala and L. Vaccaro, *Green Chem.*, 2024, **26**, 11016–11018.
23 C. Caldeira, E. Abbate, C. Moretti, L. Mancini and S. Sala, *Green Chem.*, 2024, **26**, 7456–7477.
24 C. Blum, B. Zeschmar-Lahl, E. Heidbüchel, H. C. Stolzenberg, K. Kümmerer, A. Becker and H. Friege, *RSC Sustainability*, 2025, **3**, 4724–4745.
25 J. de Verteuil, P. G. Jessop and A. Bongers, *J. Chem. Educ.*, 2024, **101**, 1592–1598.
26 S. M. Mercer, J. Andraos and P. G. Jessop, *J. Chem. Educ.*, 2012, **89**, 215–220.
27 M. Eissen and J. O. Metzger, *Chem. – Eur. J.*, 2002, **8**, 3580–3585.
28 K. Van Aken, L. Strekowski and L. Patiny, *Beilstein J. Org. Chem.*, 2006, **2**, 3.
29 S. M. Kernaghan, T. Coady, M. Kinsella and C. M. Lennon, *RSC Sustainability*, 2024, **2**, 578–607.
30 F. Roschangar, Y. Zhou, D. J. C. Constable, J. Colberg, D. P. Dickson, P. J. Dunn, M. D. Eastgate, F. Gallou, J. D. Hayler, S. G. Koenig, M. E. Kopach, D. K. Leahy, I. Mergelsberg, U. Scholz, A. G. Smith, M. Henry, J. Mulder, J. Brandenburg, J. R. Dehli, D. R. Fandrick, K. R. Fandrick, F. Gnad-Badouin, G. Zerban, K. Groll, P. T. Anastas, R. A. Sheldon and C. H. Senanayake, *Green Chem.*, 2018, **20**, 2206–2211.
31 F. Roschangar, J. Li, Y. Zhou, W. Aelterman, A. Borovika, J. Colberg, D. P. Dickson, F. Gallou, J. D. Hayler, S. G. Koenig, M. E. Kopach, B. Kosjek, D. K. Leahy, E. O'Brien, A. G. Smith, M. Henry, J. Cook and R. A. Sheldon, *ACS Sustainable Chem. Eng.*, 2021, **10**, 5148–5162.
32 S. Armenta, S. Garrigues and M. de la Guardia, *TrAC, Trends Anal. Chem.*, 2015, **71**, 2–8.
33 L. H. Keith, L. U. Gron and J. L. Young, *Chem. Rev.*, 2007, **107**, 2695–2708.
34 A. Gałuszka, Z. M. Migaszewski, P. Konieczka and J. Namieśnik, *TrAC, Trends Anal. Chem.*, 2012, **37**, 61–72.
35 J. Płotka-Wasylka, *Talanta*, 2018, **181**, 204–209.
36 F. Pena-Pereira, W. Wojnowski and M. Tobiszewski, *Anal. Chem.*, 2020, **92**, 10076–10082.

37 J. Płotka-Wasylka and W. Wojnowski, *Green Chem.*, 2021, **23**, 8657–8665.
38 W. Wojnowski, M. Tobiszewski, F. Pena-Pereira and E. Psillakis, *TrAC, Trends Anal. Chem.*, 2022, **149**, 116553.
39 N. Manousi, W. Wojnowski, J. Płotka-Wasylka and V. Samanidou, *Green Chem.*, 2023, **25**, 7598–7604.
40 P. M. Nowak, W. Wojnowski, N. Manousi, V. Samanidou and J. Płotka-Wasylka, *Green Chem.*, 2025, **27**, 5546–5553.
41 C. Capello, S. Hellweg and K. Hungerbühler, *Green Chem.*, 2007, **9**, 927–934.
42 D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada and P. J. Dunne, *Green Chem.*, 2016, **18**, 288–296.
43 P. M. Nowak, *Green Chem.*, 2025, **27**, 6699–6710.
44 T. V. T. Phan, C. Gallardo and J. Mane, *Green Chem.*, 2015, **17**, 2846–2852.
45 M. J. Eckelman, M. S. Moroney, J. B. Zimmerman, P. T. Anastas, E. Thompson, P. Scott, M. McKeever-Alfieri, P. F. Cavanaugh and G. Daher, *Green Chem.*, 2022, **24**, 2397–2408.
46 M. U. Luescher and F. Gallou, *Green Chem.*, 2024, **26**, 5239–5252.
47 L. M. de Souza Mesquita, L. S. Contieri, F. A. e Silva, R. H. Bagini, F. S. Bragagnolo, M. M. Strieder, F. H. B. Sosa, N. Schaeffer, M. G. Freire, S. P. M. Ventura, J. A. P. Coutinho and M. A. Rostagno, *Green Chem.*, 2024, **26**, 7743–7765.
48 P. M. Nowak, *Green Chem.*, 2023, **25**, 3050–3071.
49 P. T. Anastas and J. B. Zimmerman, *Environ. Sci. Technol.*, 2003, **37**, 94A–101A.
50 M. Madani, S. Hosny, D. M. Alshangiti, N. Nady, N. Alkhursani, H. Alkhaldi, S. A. Al-Gahtany, M. M. Ghobashy and G. A. Gaber, *Nanotechnol. Rev.*, 2022, **11**, 731–759.
51 G. Grillo, G. Capaldi, K. Radošević, Ž. Jakopović, K. Markov, M. Brncic, L. Gallina, E. Calcio Gaudino and G. Cravotto, *Antioxidants*, 2023, **12**, 1796.
52 G. Capaldi, C. Aimone, E. Calcio Gaudino, K. Radošević, M. Bagović, G. Grillo and G. Cravotto, *Int. J. Mol. Sci.*, 2024, **25**, 11032.
53 G. Grillo, V. Gunjević, K. Radošević, I. Radojčić Redovniković and G. Cravotto, *Antioxidants*, 2020, **9**(11), 1069.
54 C. Cravotto, A.-S. Fabiano-Tixier, M. Bartier, O. Claux and S. Tabasso, *Sustainable Chem. Pharm.*, 2024, **39**, 101509.
55 E. Tommasi, G. Cravotto, P. Galletti, G. Grillo, M. Mazzotti, G. Sacchetti, C. Samorì, S. Tabasso, M. Tacchini and E. Tagliavini, *ACS Sustainable Chem. Eng.*, 2017, **5**, 8316–8322.
56 A. Arias, G. Feijoo and M. T. Moreira, *J. Cleaner Prod.*, 2023, **418**, 137925.
57 D. Pérez-Almada, Á. Galán-Martín, M. del M. Contreras and E. Castro, *Sustainable Energy Fuels*, 2023, **7**, 4031–4050.
58 H. A. Alalwan, A. H. Alminshid and H. A. S. Aljaafari, *Renewable Energy Focus*, 2019, **28**, 127–139.
59 R. Katakojwala and S. Venkata Mohan, *Curr. Opin. Green Sustainable Chem.*, 2021, **27**, 100392.
60 A. Patel and A. R. Shah, *J. Bioresour. Bioprod.*, 2021, **6**, 108–128.
61 L. Goswami, R. Kayalvizhi, P. K. Dikshit, K. C. Sherpa, S. Roy, A. Kushwaha, B. S. Kim, R. Banerjee, S. Jacob and R. C. Rajak, *Chem. Eng. J.*, 2022, **448**, 137677.
62 Secretariat of the Convention on Biological Diversity, *Nagoya Protocol*, United Nations, 2011.
63 Secretariat of the Convention on Biological Diversity, *Convention on Biological Diversity*, United Nations, 1992.
64 Food and Agriculture Organization of the United Nations, FAOSTAT Statistical Database, accessed 2025.
65 M. Kircher, E. Aranda, P. Athanasios, I. Radojcic-Rednovnikov, M. Romantschuk, M. Ryberg, G. Schock, S. Shilev, M. D. Stanescu, J. Stankeviciute, J. Surmacz-Górska, A. Tsipa, M. Vasquez, M. Villano and C. E. Vorgias, *EFB Bioecon. J.*, 2023, **3**, 100051.
66 B. F. Oliveira, F. C. Moore and X. Dong, *Commun. Biol.*, 2022, **5**, 628.
67 J. Luo, Z. Yang, X. Huang, J. Cai and H. Zhong, *Ind. Crops Prod.*, 2025, **226**, 120738.
68 M. R. Gigliobianco, M. Cortese, S. Nannini, L. Di Nicolantonio, D. Vargas Peregrina, G. Lupidi, L. A. Vitali, E. Bocchietto, P. Di Martino and R. Censi, *Antioxidants*, 2022, **11**, 768.
69 L. Gallina, C. Cravotto, G. Capaldi, G. Grillo and G. Cravotto, *Processes*, 2022, **10**, 2233.
70 Y. Marcus, *Separations*, 2018, **5**, 4.
71 A. S. Yazdi, *TrAC, Trends Anal. Chem.*, 2011, **30**, 918–929.
72 R. Cai, Y. Yuan, L. Cui, Z. Wang and T. Yue, *Trends Food Sci. Technol.*, 2018, **79**, 19–27.
73 P. Y. Quintas, E. F. Fiorentini and L. B. Escudero, *Remediation of Heavy Metals*, Springer, 2021, 70, 351–372.
74 European Parliament and Council of the European Union, *Off. J. Eur. Union*, 2006, **L396**, 1–849.
75 International Labour Office, *Guidelines on Occupational Safety and Health Management Systems (ILO-OSH 2001)*, 2001.
76 R. A. Sheldon, *ChemTech*, 1994, **24**, 38–47.
77 P. M. Nowak, R. Wietecha-Posłuszny, J. Płotka-Wasylka and M. Tobiszewski, *Green Anal. Chem.*, 2023, **5**, 100056.
78 J. Scheffczyk, L. Fleitmann, A. Schwarz, M. Lampe, A. Bardow and K. Leonhard, *Chem. Eng. Sci.*, 2017, **159**, 84–92.
79 S. Linke, K. McBride and K. Sundmacher, *ACS Sustainable Chem. Eng.*, 2020, **8**, 10795–10811.
80 MyAssays Ltd., MyCurveFit Online Tool, accessed 2025.
81 J. H. Clark, T. J. Farmer, A. J. Hunt and J. Sherwood, *Int. J. Mol. Sci.*, 2015, **16**, 17101–17159.
82 R. A. Sheldon, J. P. M. Sanders and A. Marinas, *Catal. Today*, 2015, **239**, 1–2.
83 I. T. Horváth, E. Cséfalvay, L. T. Mika and M. Debreczeni, *ACS Sustainable Chem. Eng.*, 2017, **5**, 2734–2740.
84 D. J. C. Constable, A. D. Curzons and V. L. Cunningham, *Green Chem.*, 2002, **4**, 521–527.
85 M. C. Unegg, K. W. Steininger, C. Ramsauer and M. Rivera-Aguilar, *J. Cleaner Prod.*, 2023, **415**, 137745.
86 G. Capaldi, A. Binello, C. Aimone, S. Mantegna, G. Grillo and G. Cravotto, *Ind. Crops Prod.*, 2024, **209**, 117906.

87 M. C. Ince, B. Benyahia and G. Vilé, *ACS Sustainable Chem. Eng.*, 2025, **13**, 2721–2734.

88 D. Dallinger and C. O. Kappe, *Curr. Opin. Green Sustainable Chem.*, 2017, **7**, 6–12.

89 Z. Xie, X. Meng, S. Yu, L. Jiang and H. Pei, *J. Cleaner Prod.*, 2023, **428**, 139364.

90 R. A. Sheldon, *Green Chem.*, 2023, **25**, 1704–1728.

91 I. N. Derbenev, J. Dowden, J. Twycross and J. D. Hirst, *Curr. Opin. Green Sustainable Chem.*, 2022, **35**, 100623.

92 J. M. Weber, Z. Guo, C. Zhang, A. M. Schweidtmann and A. A. Lapkin, *Chem. Soc. Rev.*, 2021, **50**, 12013–12036.

93 Y. Ma, S. Gao, N. Mehta, Q. Fu, W. Li and B. Benyahia, *Green Chem.*, 2025, **27**, 12621–12641.

94 W. Alloun and C. Calvio, *Fermentation*, 2024, **10**, 126.

95 J. Ma, J. Yao, X. Ren, Y. Dong, R. Song, X. Zhong, Y. Zheng, D. Shan, F. Lv, X. Li, Q. Deng, Y. He, R. Yuan and G. She, *Green Chem.*, 2023, **25**, 3057–3068.

96 T. Berners-Lee, J. Hendler and O. Lassila, *Sci. Am.*, 2001, **284**, 34–43.

97 Y. Zhao, X. Li, S. Zhou, Y. Liu and H. Huang, *Green Chem.*, 2023, **25**, 3040–3048.

98 B. Pomeroy, F. Bezzo and N. Shah, *Renewable Sustainable Energy Rev.*, 2022, **158**, 112139.