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Critical analysis of green extraction techniques used for botanicals: Trends, priorities, and optimization strategies-A review

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ABSTRACT

Botanicals are widely used and marketed as food supplements or cosmetics with particular benefits for human health. Botanicals are products manufactured using natural components derived from plants, algae, fungi or lichens. Given the easy accessibility of such products, it is essential to ensure their safety by guaranteeing the absence of chemical or microbiological contamination. Furthermore, since botanicals are derived from natural products, they consist of a set of molecules called a phytocomplex, and it is important to develop standardized methods to ensure their reproducibility. Traditional approaches to the extraction of phytochemicals, as described in the monographs or pharmacopoeias of international authorities, guarantee product integrity with low levels of impurities and degradation products, but use large quantities of organic solvents with long timescales, high costs and environmental impact. A green chemistry approach is preferable to improve consumer safety, improve the extraction process and preserve the environmental status. This can be achieved by using advanced extraction methods that have proven effective in the extraction of natural molecules, such as microwave-assisted extraction (MAE), ultrasound-assisted extraction (UAE), supercritical fluid extraction (SFE) and pressurized liquid extraction (PLE) combined with GRAS solvents or unconventional solvents, such as natural deep eutectic solvents (NADES). In the chemistry of natural products, the extraction phase is a fundamental step and the one most responsible for environmental sustainability. There are usually many parameters that need to be monitored and optimized to ensure the optimized conditions of these techniques. More than the empirical one variable at a time (OVAT) approach, Design of Experiments (DoE) is required to understand the effects of multidimensionality and interactions of input factors on the output responses of the extraction phase. To date, there are no specific metrics for the extraction phase, therefore, it is necessary to identify the parameters responsible for the environmental impact of the extraction phase and to optimize them in order to increase the eco-sustainability of the analytical process. The actual review provides a critical analysis of the current green extraction procedures in natural product chemistry aimed to provide insights into strategies to improve both extraction efficiency and eco-sustainability.

1. Introduction

The diffusion of products labelled as botanicals become widely available on the global market in the form of food supplements or cosmetics ensuring the claims of their possible health benefits in the mitigation, treatment, or prevention of disease in humans. The authorities controlling the risk associated with food chain production, as European Food Safety Authority (EFSA) and Food and Drug Administration (FDA), define the connotation of food derivative products. In detail, a botanical product is a preparation made with naturally derived components from plants, algae, fungi or lichens. The market channels of these products are largely diffused through direct and online channel marketing making them easily accessible to consumers. While most of these products have a long history of use in Europe, some concerns exist about their safety and quality. These include the risk of chemical or microbiological contamination and the need to ensure that concentrations of bioactive agents are within safe limits. In the European Union (EU) the discussion about regulation of the botanical products started in 2004, and in 2009, EFSA's Scientific Committee draw up a guidance document for the safety assessment related to the use as ingredients in food supplements and the

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related botanical formulations [1]. The document focus on the necessity of a detailed characterisation of the range of products on the market and for harmonizing risk assessment and consumer information approaches. The wide range of natural molecules occurring in the phytocomplex requires a detailed standardization of the extracts [2]. A detailed analysis of chemical composition may reveal the qualitative and quantitative profile of the extracts providing a preliminary evaluation of toxicity related to the compounds potentially employed in food supplements or to the solvents used for the extraction. Moreover, the selection of suitable solvents or methods of extraction affects the recovery yield of bioactive compounds. The traditional approaches for the extraction of phytochemicals from plant are reported in the monographs of pharmacopoeia of the international authorities to guarantee the integrity of the product with low impurities and degradation products [3]. Generally, organic solvents are extensively used in the traditional protocols causing environmental impact along with time-consuming, and high-cost disposal processes.

A green chemistry approach is preferable to enhance the safety of consumers and the preservation of environmental status in the changing future toward a "one health" view [4]. The shift of chemistry toward the use of sustainable tools provides new challenges for a rational combination of eco-friendly and less energy-consuming and cheaper methodologies in analytics [5]. To meet this challenge, a large set of alternative and non-conventional solvents as natural deep eutectic solvents (NADESs) and extraction techniques are available. Actually, the namely used techniques for the extraction of natural products and botanicals are microwave assisted extraction (MAE), ultrasound assisted extraction (UAE), supercritical fluid extraction (SFE), pressurized liquid extraction (PLE) are advanced extraction methods proven for the effective extraction of bioactive compounds from plant-based matrices and products [6] in response to the potential use of natural molecules in products for human use and the climate emergency. The mentioned techniques are not green by themselves but the innovation in the technological progress of the advanced extraction methods requires the control and optimization of several parameters to rise the extraction yield of selected compounds reducing the time of extraction, health hazardousness, and environmental impact. Solvent selection, time duration, operating temperature and pressure, and flow rates of the extraction processes are the main variable to be set. The large set of parameters control requires the necessity of new protocols and procedures with uniformed conditions to standardize the extraction of each natural matrix. Generally, two approaches for the optimization of the condition are performed. "one variable at a time" is a robust and empirical approach but a long time to set each parameter is required. On the other hand, a rational approach may be employed as a Design of Experiments (DoE), considered a faster and more structured approach to design experiments for the investigation of input parameters (predictor variables) and the generated output (response variables), as well as various interactions that may exist between the input variables performed by statistical software [7]. Both approaches are more and more used to optimize the variables in a green chemistry view. The actual review provides a comprehensive overview of the procedures and a collection of set parameters for green extraction strategies focusing on the plant-based matrices used to produce botanicals with health-promoting effects. A critical analysis of advanced methodologies and a discussion of the workflows to get optimized conditions are provided in the field of natural compounds and botanical products with industrial relevance. In addition, the problem of evaluating greenness in extraction procedures was addressed, providing a brief overview of popular Green Analytica Chemistry metrics used to evaluate the environmental impact of analytical procedures. For this review, peer-reviewed literature up to 2023 were searched using Google Scholar, PubChem and SciFinder (v2023). A total of 1045 studies were identified using the keywords "botanical products", "green extractions", "ultrasound-assisted extraction", "microwave-assisted extraction", "supercritical fluid extraction", "enzyme-assisted extraction", "pressurized liquid extraction", "experimental design", "green solvents" and "life cycle assessment". A total of 39 English language papers were selected for data discussion. Papers not related to plant matrices and those using non-sustainable extraction techniques were excluded from the search.

2. Critical analysis of extraction methods

2.1. Trends and overview of the advanced extraction methods

The conventional extraction techniques that are widely used for the extraction of botanicals, (i.e. Soxhlet extraction, maceration, decoction, infusion, and percolation methods), have several disadvantages as low selectivity, generally require long extraction times is generally required, and large amounts of organic solvents used give rise to safety risks for operators and the surrounding environment [8–10].

Conventional extraction methods are usually based on the diffusion of natural substances from a solid matrix to a liquid phase (i.e. maceration, percolation). The exhaustiveness of the extractions is guaranteed by several cycles that are subsequentially performed within time-consuming protocols. Some of the techniques require the use of higher temperatures (i.e. decoction, infusion, heating reflux extraction) and/or mechanical forces to favourite the compound releasing (heat and stirring) with a wide energy demand.

Hence the use of emerging green extraction techniques for the extraction of phytocomplex and natural compounds are spreading to reduce the environmental impact of the extraction process and at the same time make the final product safer for human daily intake. The choice proper extraction techniques is based on a preliminary evaluation of the advantages or limitations related to the performance of the extraction tools and the chemical nature of the target compounds [11]. Nowadays, researchers and industries are increasingly focusing on developing and adopting green extraction methods to meet the growing demand for sustainable and environmentally friendly practices in extraction These extraction methods include microwave assisted extraction (MAE), supercritical fluid extraction (SFE), pressurized liquid extraction (PLE), ultrasonic-assisted extraction (UAE), enzyme assisted extraction (EAE), and pulsed electric field extraction (PEFE) used with a positively increasing trend in the scientific literature about the field of food and plant analysis (Fig. 1). Generally, the green extraction techniques refer to processes that are designed to minimize environmental impact and reduce the use of hazardous solvents or chemicals in extracting valuable compounds from natural sources. These techniques offer several advantages over traditional extraction methods, short extraction time, reduced volume of hazardous organic solvents, recovery of higher extraction yield, and automatization of the procedure ensuring the reproducibility of the extraction process with lower energy consumption [12]. With the aim to choose the appropriate technique, a detailed discussion about the advantages and limitations of each

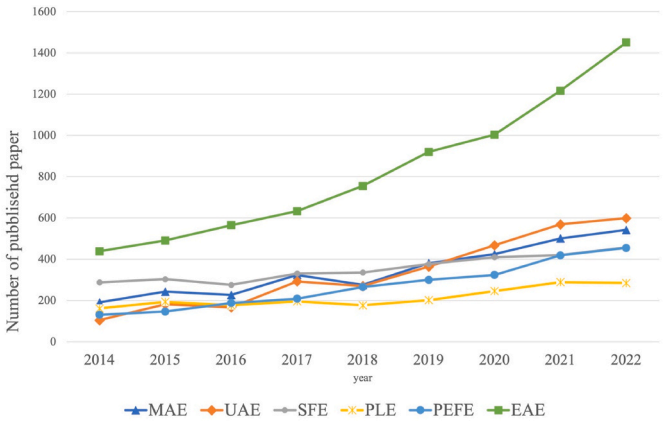

Fig. 1. Trend of advanced extraction methods from 2014 to 2022.

technique is reported in the following paragraph and detailed in Table 1.

Supercritical fluid extraction (SFE) is a separation technique used to extract desired components from various substances using supercritical fluids as the extracting solvent. SFE (Fig. 2) uses fluids in supercritical state, a state of matter that exists above its critical temperature and critical pressure where its exhibiting both liquid and gas-like properties [13]. Each gas or molecule in the specific condition of pressure and temperature lay in the supercritical state possessing a density like a liquid but can pass through porous solids such as a gas. Supercritical fluids mimic solvation power, low viscosity, and high diffusivity enhancing diffusion and mass transfer for a reduced time extraction process [14]. The most used supercritical fluid in food processing, essential and herbal extraction is carbon dioxide (SFE-CO_2) due to its relatively low critical temperature and pressure, making it safe and effective for many applications. Other advantages, in the use of CO_2 as common supercritical fluid are the cheapness, availability in pure form, and unhazardous in a monitored environment. Usually, a temperature upper to the critical point of the selected extractant has been employed in supercritical fluid extraction with the aim of decreasing the solvent density and solvation power while improving the solute vapor pressure, therefore enhancing the extraction yield of compounds reflecting the polarity in that condition [14]. However, scientific validation of temperature and pressure parameters is highly recommended to optimize extraction procedures. Moreover, the addition of co-solvents (i.e. water and ethanol) enhances the solubility of more polar compounds in the carbon dioxide [15]. The SFE-CO_2 method offers several advantages over traditional extraction techniques: First of all, adjusting the temperature and pressure, it is possible the selective extraction of specific components avoiding the co-extraction of others interfering substances. This is especially useful when extracting valuable bioactive compounds from complex mixtures. SFE-CO_2 is solvent-free and does not leave harmful residues in the extracted product, making it more environmentally friendly and safer for human consumption. The process operates at relatively low temperatures, which helps to avoid the degradation of heat-sensitive compounds that may degrade under high temperatures commonly used in other extraction methods. Finally, after the extraction, the supercritical fluid can be easily removed from the extract by reducing the pressure. This results in a pure, solvent-free extract that is ready for use without the need for additional purification steps. SFE-CO_2 is particularly suitable for the extraction of high molecular weight apolar compounds, but it is possible to increase the solubility of more apolar compounds in carbon dioxide by the addition of co-solvents (e.g. water and ethanol) [11], thus improving the extraction yield from complex matrices. A study carried out by Rajaei for the recovery of tea seed oil compared SFE-CO_2 extraction with the conventional Soxhlet technique. The results showed an extraction yield of about 16.4% after SFE with pure CO_2 compared to Soxhlet extraction which was 30.3%. However, the addition of 15% EtOH made it possible to reach the Soxhlet extraction yield, improving sustainability and avoiding the use of toxic solvents (petroleum benzene) [16]. A comparison of different techniques for extracting oil from eucalyptus leaves also showed SFE-CO_2 to be a viable alternative to conventional techniques. The results showed that hydrodistillation had the lowest yield and the extract obtained contained only polar compounds, whereas extraction with Soxhlet and SFE-CO_2 also recovered high molecular weight and low polarity compounds. The addition of ethanol to SFE-CO_2 also increased the oil yield obtained by Soxhlet extraction [17]. Finally, a study by Popescu et al., showed that supercritical methods allow a greater extraction of lycopene (1016.94 mg/100 g extract) than Soxhlet extraction with ethyl acetate (454.54 mg/100 g extract), more than 2-fold [18,19], showing the efficacy and selectivity of supercritical fluid extraction.

Microwave-assisted extraction (MAE) (Fig. 2) is a modern extraction technique used to isolate compounds from various samples using microwave energy. The method exploits the interaction between microwave radiation, which generates electromagnetic waves with a frequency typically ranging from 300 MHz to 300 GHz and the target material to enhance the extraction process from food and agro-industrial by-products [20]. The microwave energy is adsorbed by the material causes the displacement of polar molecules creating dipole rotation, driving the molecules to align to the existing electric field, leading to internal heat generation resulting in the breaking of chemical bonds that facilitate the extraction process [21]. MAE often requires minor volume

Table 1
Advantages and limitation of enhanced extraction techniques.

Extraction technique	advantage	disadvantage	references
Microwave-Assisted Extraction (MAE)	- Rapid extraction time -Low energy consumption -Low costs of the equipment -Solvent is not necessary	-Uncontrolled heating of sample may affect extraction efficiency of heat-labile compounds -Non-selective extraction -Short penetration depth of microwave upon scaling up	[20–22, 50]
Supercritical Fluid Extraction (SFE)	-High selectivity by the control of temperature and pressure affecting solvation power -Mass transfer and higher extraction yield enhanced by low viscosity and high diffusion rate of supercritical fluids -Recovery of heat-labile compounds operating at mild temperatures -Gas depressurization assists the recovery of extracted compounds, also in the presence of low ratio solvent -Recyclability of supercritical fluid.	-High cost of the equipment -Complex configuration of the system -Strict environmental monitoring for gas releasing -Low selectivity towards polar compounds.	[8,15,51]
Pressurized Liquid Extraction (PLE)	-Reduced extraction time; -Low amount of solvent required -Use of solvents with different polarity or mixtures for the recovery of large-range polarity molecules -Easy to scale up process	-high cost of the equipment -rigorous optimization of extraction parameters temperature and pressure -heating for a long time may cause the degradation of thermolabile compounds	[28,52]
Ultrasound-Assisted Extraction (UAE)	-Low energy consumption -Rapid extraction time -Low amount of solvent	-Non-selective extraction; -thermal degradation of the heat-labile compound; -the aging of the instrument decreases ultrasound intensity, thus reducing the reproducibility	[21, 33–35,53]
Enzyme-Assisted Extraction (EAE)	-Uses water as solvent. -Suitable to separate bound compounds.	-Enzyme sensitivity. -Difficult to scale up to industrial applications. -Expensive price of enzyme for large volume of samples	[40]
Pulsed Eelctric Field Extraction (PEFE)	-Rapid extraction time -Low-temperature performance -Extraction of heat-lable molecules;	-High costs for maintenance. -Accurate control of parameters.	[38]

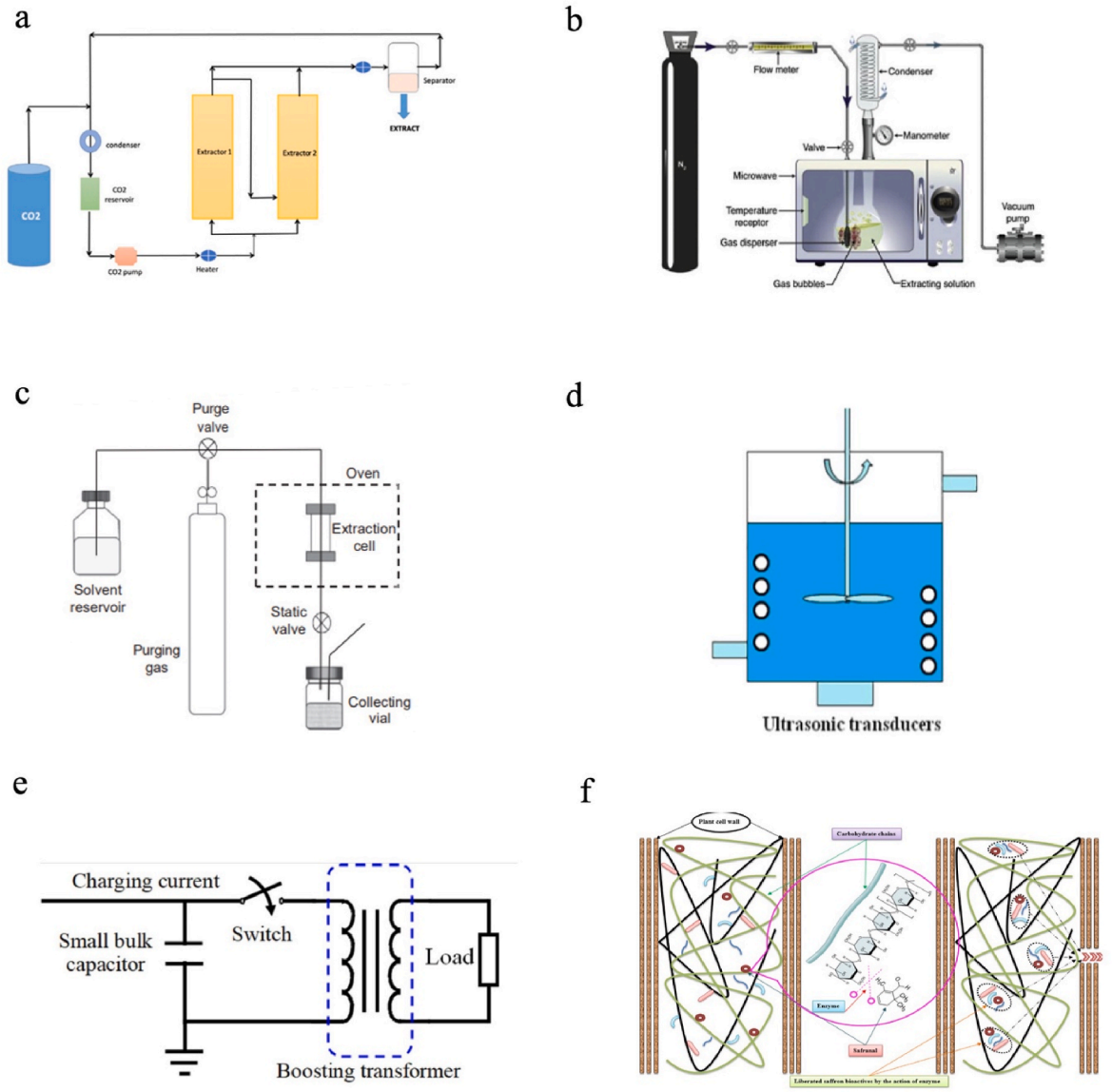

Fig. 2. Graphical explication of principles and equipment of advanced extraction techniques: (a) SFE flow diagram [6]; (b) MAE flow diagram [12]; (c) PLE flow diagram [15]; (d) UAE flow diagram [19]; (e) PEFE flow diagram [20]; (f) EAE flow diagram [21].

of solvent, the procedure of extraction can even be performed in the absence of solvent where naturally occurring water of the sample acts as a solvent and facilitates cell lysis [22]. Despite its advantages, microwave-assisted extraction may not be suitable for all types of samples, and optimization of extraction conditions is crucial to achieving the best results for each specific application. Several studies have been reported in the literature that favour the MAE technique over other approaches, particularly conventional extraction. Galan et al. compared MAE with conventional solvent extraction (CSE) of polyphenols from dried sea buckthorn leaves and found that MAE gave a higher yield of TPC (162 mg GAE/g plant material) and antioxidant power (93.6 ± 0.5 μmol Trolox/g plant material) than CSE under the same extraction conditions (150 mg GAE/g TPC and 71.5 ± 1.0 μmol Trolox/g) [23]. Da Rosa et al. compared MAE with maceration of polyphenols from dried olive leaves. MAE extraction was more efficient in terms of phenolic yield (TP), with an 82% increase compared to maceration. This effect seems to be mainly due to the temperature contribution in the extraction process, making MAE a suitable and faster alternative to organic solvent maceration [24]. Similarly, Rafiee et al. reported a 46% increase in TP yield from *Olea europaea* L. leaves using MAE with water and an extraction time of 4 min compared to maceration with water for 24 h at room temperature [25]. Finally, Pal and Jadeja used response surface methodology (RSM) to maximise the extraction of phenolic compounds from onion peels using MAE with NADES. Under optimum conditions, the recovery of phenolic compounds was 80.45 mg GAE/g dry weight (DW) and the maximum reducing power activity was 636.18 μmol AAE g/DW. The phenolic content was higher than maceration (63.28 mg GAE/g extract) and methanolic Soxhlet extract (54.73 mg GAE/g extract) and was achieved with a 12-fold reduction in extraction time [18,26]. Therefore, the interaction of microwaves with solvent molecules, causing an increase in temperature and pressure within the plant material, may promote wall rupture and release of molecules [27].

Pressurized liquid extraction (PLE) also known as accelerated solvent extraction (ASE) enhanced solvent extraction employs solvent in the subcritical condition of high temperature and pressure from solid and semisolid samples [28]. Under high pressure, organic solvents are maintained close to the supercritical regions of the phase diagram remaining in the liquid state [29]. This state allow the solvent to diffuse into the sample matrix, modify dielectric constant of used solvent, and

allow the reduction of surface tension, viscosity of the solvent, ensuring an easier mass transfer rate and diffusion, and decreasing the extraction time and solvent consumption (Fig. 2) [28]. To date, PLE is a widely used technique to improve extraction yields and recovery of bioactive compounds. As there are several parameters (temperature, number of cycles, extraction time and solvent composition) that can significantly affect PLE extraction, it is important to optimize the process to maximise bioactive recovery and improve extraction efficiency. Chada et al. [30] optimized the PLE parameters (90 °C, ethyl acetate:ethanol, 50:50 v/v, 50 min, 2 mL/min) to obtain tomato pomace extracts with high antioxidant activity (19.10 μmol TE/g) and lycopene content (20.09 μg/g), with an increase over Soxhlet extracts with ethyl acetate for 6 h (18.43 μmol TE/g and 10.75 μg lycopene/g), especially improving lycopene recovery [18]. There are several studies in the literature using PLE for the recovery of bioactive metabolites from plant matrices, with particular interest in the polyphenol class, with results even superior to those obtained with conventional techniques. For example, Viganó and colleagues compared PLE with other conventional extraction techniques (Soxhlet and maceration) for the recovery of phenolic compounds from passion fruit. The results showed that the extraction yield and phenolic content of PLE extracts were higher than maceration and Soxhlet and in a shorter time [31]. Again, the results of blackberry (*Rubus fruticosus* L.) obtained from Da Fonseca Machado et al., show that PLE (under the best extraction conditions) is much more effective in terms of total % extraction yield (6.33 ± 0.04) and phenolic content (7.36 ± 0, 18 mg GAE/g FR) and antioxidant capacity (76.03 ± 1.05 DPPH and 68.28 ± 2.68 μmol TE/g FR ABTS) than maceration (5.02 ± 0.07 yield and 3.66 ± 0.05 mg GAE/g FR, 29.04 ± 2.18 DPPH and 46.09 ± 1.15 μmol TE/g FR ABTS). The combined application of high pressure and temperature in PLE is therefore very effective and often better than conventional techniques for the recovery of anthocyanins, phenols and other metabolites from various sources [32].

Ultrasounds propagate in a series of compression and rarefaction waves that disperse through the molecules of the medium. In detail, at high-intensity rarefaction cycles any cavitation bubbles are formed in the molecules of the medium which cause disruption of cellular structures and facilitate solvent penetration [21,33]. The cavitation of the medium is related to the physical properties of the solvent, such as viscosity, surface tension, and saturation vapor pressure. Furthermore, the mass transfer is enhanced by the releasing of energy in the form of heat [21,34]. The mechanical phenomena associated to ultrasound-assisted extraction cause cell wall disruption and degradation of plant matrix and enhance mass transfer by the reduction of particle size (Fig. 2) [35]. This improves the extraction yield of many compounds and is also important for the recovery of bioactive from botanicals. In particular, numerous application studies have been reported in the literature to increase the extraction yield of phenols. In a study conducted by Jovanovic [36], UAE increased the recovery of polyphenols from *Serpylli herba*. The results showed that the total phenolic content (TPC) was significantly higher in extracts obtained by UAE than in extracts obtained by maceration and HAE. After 5 min of UAE, the amount of TPC was 17.3% higher than in extracts obtained by HAE. The TPC obtained by UAE after 5 min of extraction was higher than that obtained by maceration after 60 min. These results highlight the ability of ultrasound to significantly reduce extraction time. For example, Akram Mousavi and co-workers increased polyphenol recovery and antioxidant capacity from *Ferulago angulata* in just 5 min compared to the 2 h required for extraction by maceration. The highest DPPH radical scavenging activity obtained was 76.57% for the maceration method, compared with 86.06% for the UAE method [37].

The pulsed electric field extraction (PEFE) is a non-thermal process made by a living cell suspension, subjected to an electric field. The electrical potential passes across the cell membrane generating a transmembrane potential. At 1 V potential, the charged molecules create pores through the membrane, increasing the permeability [38]. PEFE enhances the extraction of metabolites from botanicals by employing less time-consuming, using less solvent, and lower temperatures of extraction compared with other extraction techniques; those advantages make PEFE a good method for industrial application (Fig. 2). Segovia et al. (2015) found that PEFE increased total phenolic content and oxygen radical absorbance capacity (ORAC) values by 2.0–13.7 times compared to the control [39].

For enzyme-assisted extraction (EAE) the plant cell wall is destructed by enzymes, such as cellulase, pectinesterase, hemicellulase, fucosyltransferase, pectinase, α-amylase, and protease allowing the internal metabolites release [40]. EAE is used when the plant matrix compounds are preserved by hydrogen or hydrophobic bonding in the polysaccharide-lignin network and are not accessible to remove using a solvent in a traditional extraction process (Fig. 2). The main factors that affect EAE are the particle size of the material, the chemical composition of the plant matrix, the type and dosage of the enzyme, strict control of time and temperature to avoid protein degradation, solvents and polarity of target compounds. The choice of solvent in EAE is important, and often depends on the type of enzyme used and the polarity of the targeted metabolites. The relative polarity of the metabolites extracted during EAE can vary widely. Enzymes are often employed to target specific classes of compounds, such as polyphenols, flavonoids, alkaloids, or proteins [41]. These compounds can exhibit a range of polarities, and the choice of solvent or solvent mixture is tailored to enhance the solubility and extraction efficiency of the targeted metabolites. Enzymes can be specific to certain substrates, and the selection of a compatible solvent is crucial for efficient extraction. The common solvents used in enzyme-assisted extraction include water, ethanol, acetone and their mixture [41]. When the target compounds are polar, water is commonly used as a solvent in EAE. Enzymes such as cellulases, pectinases, and proteases are commonly used in combination with water to break down cell walls and release bioactive compounds [41]. Ethanol is used for the extraction of broad range of bioactive compounds, including polyphenols, flavonoids, and alkaloids [42]. The choice of ethanol concentration can be adjusted based on the polarity of the targeted metabolites. The optimization of the extractions of wide range of metabolites with different polarities may be improved using solvent mixture as ethanol-water. Acetone is another solvent that can be used in enzyme-assisted extraction. It is effective for extracting a variety of polar and nonpolar compounds [43–45]. However, acetone should be used with extremely caution as it could denature the enzymes used. Many scientific studies have been published on the separation of biologically active compounds from plant materials using EAE. In their research on the extraction of lycopene from sources such as tomatoes, Choudhari and Ananthanarayan investigated how cellulases and pectinases affect the extraction process to achieve a higher yield [46]. According to Boulila et al., the application of cellulase, hemicellulase, xylanase and their ternary mixture could increase the yield of essential oil extraction from bay leaves [47]. Using a mixture of α-amylase and amyloglucosidase enzymes, researchers were able to increase the extraction yield of curcumin from turmeric [48]. For example, EAE was used to extract a carotenoid-rich fraction from red chilli (Capsicum annuum) with the highest carotenoid content of 30.37 mg/100 g fresh weight [49].

2.2. Eco-sustainability assessment of green extractions in natural product chemistry

The biggest environmental challenge in chemistry and especially in natural product chemistry is compliance with the 12 principles of Green Analytical Chemistry (GAC), established a decade ago [54]. GAC is an analytical chemistry approach that focuses on reduce or eliminate hazardous substances of analytical methods and processes, minimize their negative impact on human health and the environment, maintaining at the same time high-quality analytical results. It emerged as a response to the increasing concern about the environmental impact of chemical analysis and the desire to make analytical practices more sustainable. The extraction of the botanicals is a key step in the natural product

chemistry, and it has been identified as one of the most critical steps from the GCA point of view because it is responsible for the consumption of solvent, energy, and consumable materials or devices.

Therefore, the choice of highly sustainable and environmentally friendly extraction procedures is a crucial step in natural product chemistry. Very often, developed procedures or products defined as "green" do not pass a heuristic assessment of sustainability [55,56].

The techniques mentioned above are considered more ecological than traditional extractions such as maceration, percolation, and Soxhlet. Although they have desirable characteristics for sustainability, it is necessary to evaluate their real environmental impact considering multiparametric metrics [55]. Therefore, it is necessary to have tools that allow us to analytically evaluate the greenness of chemical processes [57]. Life Cycle Assessment (LCA) is a holistic tool that allows the evaluation of the potential environmental impacts of products and processes along their life cycle, using an input-output approach [58]. The life cycle of a product typically includes various stages, starting from the extraction of raw materials, through production and use, to its eventual disposal or recycling. LCA considers materials, energy, and emissions, at each stage of the product's life cycle. One of the major challenges in evaluating green chemistry technologies is gathering the desired data for LCA. Therefore, quantitative metrics are needed to identify the parameters to be monitored in an analytical procedure [59]. Metrics need to be specific and detailed enough to provide useful information about the chemical product or process, but they also must be simple enough to address the environmental issues within a useful time frame [59].

In the last few years, several metrics for evaluating the greenness of analytical procedures have been developed [57,60]. The first analytical metric tool proposed was the pictograms of NEMI. The latter turned out to be a simple approach based on a four-field circle, where each field represented a different aspect of the analytical procedure. Each field to be labelled green must meet certain criteria: the chemical substances used must not be classified as persistent, bioaccumulate and toxic (first field), not belong to lists of hazardous waste D, F, P, or U (second field), the sample pH must not be corrosive (third field) and the amount of waste generated must not exceed 50 g (fourth field) [57]. Although NEMI is a simple and intuitive approach, it is a very generic and semi-quantitative tool. Subsequently in 2012, an Analytical Eco-Scale metric tool was proposed, which still today is the most used approach to evaluate the greenness of analytical methods [57]. Analytical Eco-Scale is based on assigning a score of 100 to an "ideal green analysis" from which penalty points are subtracted when solvents or reagents cause environmental and human health problems, energy consumption exceeds 0.1 kWh and waste is generated [61]. Over the years, the growing need to quantify the real environmental impact of analytical procedures has prompted the development of advanced metric tools such as the Green Analytical Procedure Index (GAPI), RGB model, Analytical GREEness Metric Approach (AGREE) and the hexagon- CALIFICAMET. These approaches are often generic and leave out phases of the analysis responsible for the no-greenness analytical procedure. For this, the development of specific metrics for crucial and problematic steps of the analytical procedure is required. Currently, specific metrics have been developed for greenness assessment of the chromatographic analysis (AMVI, HPLC-EAT, and AMGS) [62–64], sample preparation phase (AGREEprep) [65]. The latter is the first tool designed for the assessment of analytical sample preparation greenness and it is based on 10 impact categories which have been recalculated in sub-scores on a 0–1 scale and then used to calculate the final evaluation score [65]. The assessment criteria are based on the ten principles of green sample preparation: the choice of the solvents, material, and reagents, the waste production, energy consumption, sample size, and throughput [65].

Until today, analogous tools for the specific assessment of the extraction step greenness are not reported in the literature. AGREEprep is the metric tool that best suits the assessment of greenness in the extraction step in natural product chemistry, but, to date, it has only been applied to the assessment of the sustainability of analytical procedures for the determination of contaminants [65].

In literature, there are still few studies regarding the assessment of the environmental impact of botanical extraction. Barjoveanu et al. have analysed the environmental performance of two lab-scale processes (Soxhlet and UAE) for the extraction of polyphenols from spruce bark by LCA methodology. The study showed that the electricity used to heat the extraction system, followed by solvent consumption and emission have contributed most to the environmental impact of both extraction processes. Although UAE has shown a lower yield, it was more eco-sustainable than Soxhlet extraction. Instead, its environmental impact was only about 20% (in most impact categories) of the impact of the NaOH extraction process [66]. Vauchel et al. have evaluated the environmental impact of different UAE extraction conditions used for the recovery of polyphenols from chicory. The extraction temperature increase and the use of ethanol were responsible for the environmental impact of the extraction processes [67]. Ding et al. have compared the environmental impact of alternative extractions and post-extraction tannin processes from Norway spruce bark by PHWE. The results showed that the extract drying process is the primary contributor to the environmental impact of tannin production [68]. Salzano De Luca et al. have combined chemical analyses and LCA to compare the efficiency and environmental sustainability of three laboratory-scale extraction techniques (conventional maceration, UAE, and MA) for the recovery of polyphenols from pine needles. The extraction time positively influences the yield of the extraction process and negatively its environmental impact, as the gains in terms of yield deriving from the extension of the extraction processes involve higher energy costs. The energy consumption measured under optimal operating conditions is 1.32×10^{-2}, 1.37×10^{-2} and 1.45×10^{-2} kWh for CM, UAE and MAE respectively. However, the calculated environmental impacts must reflect not only the different energy consumption of the three methods, but also their extraction efficiency. Therefore, when looking at the normalised energy consumption in terms of efficiency, even greater differences between the extraction techniques were found: 2.69×10^{-3}, 3.01×10^{-3} and 4.67×10^{-3} kWh mg GAE $^{-1}$ for CM, UAE and MAE respectively. At the same time, it must be recognised that the efficiency of a given extraction technique can be extremely variable. Following the same approach, the authors recalculated the potential impacts assuming the same extraction efficiency for CM, UAE and MAE (i.e. TPC of 1 mg GAE g PN $^{-1}$). The differences in the potential impact stabilised cumulative results of the individual results are 5.68×10^{-6}, 5.75×10^{-6} and 5.85×10^{-6} Pt for CM, UAE and MAE respectively. Overall, these results show that the use of energy-intensive extraction methods such as UAE and especially MAE is only environmentally worthwhile if they effectively guarantee higher yields in significantly shorter processing times than conventional methods. Even the choice of "greener" solvents (ethanol *vs* acetone) appeared questionable, as the extraction yield has a greater impact than the "green" of the raw materials (single score indicators using ethanol instead of acetone are 4–6 times higher) [69]. Pappas et al. have analysed and compared the environmental impact of five extraction techniques (PEF, UAE, MAE, boiling water extraction, and maceration), by LCA for the recovery of polyphenols from *Moringa oleifera* leaves. The results show that PEFE, MAE and maceration have a lower environmental impact than UAE and BW systems for the production of 1 kg of polyphenols. The amount and origin of the electricity used contribute significantly to the environmental impact for all techniques, it is evident that replacing the electrical source with PV arcs reduces the overall environmental impact score (eco index Pt), in particular the overall scores were 26.718349 (PEFE), 26.718349 (MAE) and 32.986533 (maceration). This result is justified by the lower energy consumption and the lower use of Moringa oleifera leaves. PEFE and MAE are more efficient (in terms of mass) and friendlier (in terms of environmental criteria) than maceration and therefore UAE and BW, demonstrating that 'green' electroporation and microwave technologies are the most

environmentally friendly for the extraction of polyphenols from Moringa oleifera leaves [70].

The choice of extraction solvent is a crucial aspect in the GAC [71]. Fratterigo Garofalo et al. have shown the sustainability of isopropanol as a non-conventional solvent for rice bran oil extraction by UAE [72]. The development of new "green" solvents is one of the strategies implemented in GCA to reduce the environmental impact of analytical laboratories activities [71]. Deep eutectic solvents (DEP) turned out to be one of the most promising alternatives to conventional extraction solvents [71]. Murugan et al. have evaluated the environmental impact of extraction of bioactive compounds from *Darcyodes rostrata* using DES and ethanol through an LCA [73].

When a laboratory-scale extraction process is transferred to an industrial scale, in addition to an LCA analysis, a techno-economic assessment is also required to determine the environmental and economic performance of the processes. Vega et al. have combined an LCA analysis with a techno-economic assessment for the analysis and improvement of the transition from laboratory to industrial scale of two extraction processes (solvent extraction and PLE). The solvent/matrix ratio and the extraction yield are the parameters that most influence the environmental and economic performance of industrial-scale processes. Although PLE shows a higher yield, it has higher economic and environmental burdens than solvent extraction on an industrial scale [74].

2.3. Criteria of selection for botanicals and related products

The exponentially increasing demand for herbal products and/or extracts for health-promoting applications in nutraceutical and medicine-based industries drives the need for fast availability of high-quality products with low costs of processing, higher yield, and safety for the operators and consumers. The design of extraction procedures requires a preliminary selection of the class of bioactive compounds and the vegetal source characterized by a high interest in the formulation of botanicals. In line with the green chemistry approach, the recovery of natural constituents is related to the choice of solvents and extraction techniques and the combination to the analytical equipment and tools used for a rational design of the experiments, extraction monitoring, and data processing. Plants are characterized by a complex secondary metabolism leading to the production of specialized compounds characterized by diverse biological functions and environmental responses [75]. The most occurring specialized metabolites are mainly ranked as polyphenols, alkaloids, polysaccharides, fatty acids, terpenes, carotenoids, essential oils, and volatile organic compounds. The selective extraction of target compounds from natural matrices follows a step-by-step selection. Moreover, the development of extraction methodologies oriented to the reduction of the environmental impact to produce health-promoting products drives the necessity to find alternative solvents and extraction procedures. Generally, the efficiencies of conventional and advanced extraction methods mostly depend on the nature of the plant matrix, the chemistry of bioactive compounds, and scientific expertise [76]. A detailed collection of green extraction procedures used for the production of plant-based formulations is provided in the following section for a driven selection of conditions for the extraction, and analysis of natural products in view of formulation of bioactive botanicals by green chemistry approach.

2.3.1. Extraction of natural compounds from botanicals

Generally, polar or non-polar fractions can be recovered from complex natural matrices. The main classes of molecules occurring in the polar fraction are ranked as phenolic compounds, often isolated as glycosidic forms. Various types of Polyphenols occur in food plants like fruits, herbs, and vegetables exerting mainly antioxidant activity for the prevention of human diseases and the support of health care. Solvents like water, methanol, ethanol, and hydroalcoholic mixtures are used to recover polyphenols in combination with traditional techniques (mainly maceration, and Soxhlet extraction) dispensing large amounts of solvent and longer time of the extraction for the recovery considerable yield of compounds. Beyond the large use of conventional procedures for the standardized recovery of polyphenolics, the advanced extraction methods perform efficient and lower costs extraction of polyphenols recovering the maximum yield of polyphenols with less amount of solvent in a shorter extraction time [14,77]. Reported experimental results highlighted that green techniques are more effective in recovering secondary metabolites. A suitable combination of green solvents and extraction techniques can be tailored for specific purposes by adopting appropriate technologies and extraction conditions to obtain a different composition of bioactive compounds in the final product from the same matrix [78].

More than polar compounds, other molecules with lipophilic behaviour as phytosterols, fatty acids, carotenoids and essential oils can be recovered from natural matrices for their bioactive effects. Phytosterols are cholesterol-like molecules occurring in food plants, with high concentrations in unrefined plant oils, nuts, and olive oils. Usually absorbed by daily food intake, phytosterols inhibit the absorption of cholesterol and recirculate endogenous biliary acids, exerting a crucial role in cholesterol elimination away the intestinal tract. Food supplements of phytosterols are currently used to reduce blood cholesterol levels and prevent coronary heart disease. Moreover, recent studies highlighted their applications in anti-inflammatory, anti-cancer, and hepatoprotective activity [79]. The conventional extraction of phytosterols include an organic phase extraction followed by acid hydrolysis to separate unsaponifiable fraction but Feng et al., 2020 reported an innovative extraction by direct saponification with the green method is performed with higher effectiveness in extraction yield and eco-sustainability process [79] opening new perspectives for unconventional green extraction as discussed in the current review.

Fatty acids are considered essential nutrients with a high bioactive profile. Food derivative fats can be generally ranked into unsaturated fatty acids (UFA), and saturated fatty acids (SFA). In particular, naturally occurring *cis*-unsaturated fatty acids can be further divided into monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) both characterized by functional roles in NCDs. In recent evidence, replacing SFA-rich foods with plant-based foods rich in UFA was associated with a lower risk of cardiovascular outcomes [80]. Several species are reported for the high content of UFA. Despite oils from olives, nuts, soybean, camellia seeds, avocado fruits, and leafy plants being commonly studied for the occurrence of monounsaturated fatty acids, many other structures remain to be discovered in the plant kingdom [81]. It was estimated that 40% of plant families were yet to be investigated for fatty acid composition [82]. Recent studies reported novel sources of bioactive lipids occurring in plants with a functional role in human health as novel candidates to produce botanical products. For instance, the comprehensive polar lipid profile of purslane was investigated, not usually occurring in leafy plants. The HPLC-HRMS/MS^n analysis highlighted a wide range of lipid classes from linear and cyclic oxylipins to glycolipids, phospholipids, and sphingolipids characterized by high molecular weight lipids. The extracts and lipid-enriched fractions of edible parts exerted *in-vitro* anti-inflammatory activity by the inhibition of the TNF-α-stimulated NF-kB pathway and the activation of PPAR-ɣ and Nrf2 transcription factors [83]. Despite the high biological and nutritional value of lipids in botanicals, conventional extraction solvents and techniques were largely used and the extraction processes of the UFA by a green approach is a challenging task. In the view of green chemistry extraction, a sequential workflow based on green procedures was performed by Vardanega et al., 2023. In particular, the inedible seeds and peel of granadilla fruit occupy a large part of the fruit (10% of total fruit weight), while its pulp is freshly consumed. The objective of the cited study was to obtain added-value bioactive compounds from granadilla seeds by preliminary recovering of SFE-CO_2 oil containing 82.37% of UFA, then a second step of PLE and UAE extractions to recover the phenolic fractions from the defatted seeds (Table 2) [84]. In line with the described green workflow, a novel way for the

Table 2
Optimized condition for the selective extraction of botanicals by green extraction techniques.

Matrix	Target compounds	Extraction technique	Specific parameter	Extraction yield	reference
Granadilla seeds	UFA oil	SFE-CO_2	40 MPa 40 °C 2 L/min (CO2)	24.97%	[84]
Granadilla seeds	Phenolics	PLE	10 MPa 70 °C 75%EtOH 30 min	13 ± 2%	[84]
R. officinalis	Terpenes	SFE-CO_2	80 bar 50 °C 1 L/min	3.3 ± 0.3%	[95]
Scutellaria incarnata	Phenols	UAE	70% EtOH 50 °C 5 min	–	[96]
Scutellaria coccinea	Phenols	UAE	50 °C 70% EtOH 15 min	–	[96]
Scutellaria ventenatii	Phenols	UAE	50 °C 40% EtOH 15 min	–	[96]
Lippia citriodora	Phenylpropanoids and flavonoids	SFE-CO_2	451 bar 57 °C 17% EtOH 90 min	73.982 μg/g DM	[97]
Syzygium cumini	Phenols	UAE	63% EtOH 60 min	86,35 ± 3,02 mg GAE g-1 EXT	[98]
Beta vulgaris	Phenols	UAE	50 °C 40 kHz 50% EtOH, 30 min	32.17%	[92]
Beta vulgaris	Phenols	MAE	10 min 600 W	37.04%	[92]
Beta vulgaris	Phenols	PLE	125 °C 50% EtOH 10 min	32.85%	[92]
Beta vulgaris	Phenols	SFE-H_2O	150 °C 10 min	28.84%	[92]
Carrot *(Daucus carota* subsp. *sativus)*	Carotenoids	MAE	50 °C 2.45 GHz 50%EtOH 5 min	19.2%	[99]
Mango peel *(Mangifera indica* L.*)*	β-Carotene	SFE-CO_2	25.0 MPa 60 °C 15% w/w ethanol	6290 mg/100 g dry peel	[100]
Tomato by-products (*Solanum lycopersicum*)	Lycopene	UAE	70 °C 120 mL/g ratio DL-menthol and lactic acid (8:1) 10 min	1.446 mg/100 g of dry sample	[101]
Pumpkin by-products (*Cucurbita maxima*)	β-Carotene	UAE	50 °C 52.5 W/cm3 Caprylic acid: Capric acid (3:1) 10 min	15,141 mg/100 g	[102]
Dendranthema indicum	Essential oils	SFE	40 °C 750 W 26 MPa 105 min	9.37%	[103]
cloves, cinnamon barks, orange and lemon peels, eucalyptus leaves, cardamom seeds	Essential oils	Solar energy-based extraction system (SEE)	1000 W/m2 solar radiation 0.65 h (clove) 0.80 h (cinnamon) 0.41 h (orange) 0.61 h (lemon) 0.39 h (eucalyptus) 0.45 h (cardamom)	13.4–15.3% (clover), 4.1–4.4% (cardamom), 3.3–3.6% (cinnamon), 3.2–3.4% (eucalyptus), 1–1.1% (lemon) and0.9–1% (orange)	[87]

manipulation of the natural matrix is opened for the application of lipid-enriched food destinated for the production of health-promoting botanicals with human consumption.

The carotenoids are ranked as isoprenoid compounds characterized by the C40 carbon skeleton. Lycopene has the basic acyclic structure showing the key feature of all carotenoids made by a central polyene chain. Complex carotenoids have the same skeleton with structural changes as cyclization of end groups (the case of β-carotene or α-carotene) and oxidized functions [85]. The family of carotenoids is reported for their functions in human health as antioxidant activity, cancer-preventing, and eye condition improvement [86]. The conventional solvents used for the extraction of carotenoids from foods is made by n-hexane: acetone: ethanol mixture in a 2:1:1 v/v ratio followed by NaOH saponification to discard the saponifiable fraction, but the development of advanced extraction methods is desirable for a more sustainable and safe approach as discussed in the current work.

Essential oils are complex mixtures of volatile compounds, easily evaporated upon heating, widely used for cosmetics, fragrances, and

aromatherapy [87]. The recovery of the high-value oils is commonly obtained by conventional methods such as hydro distillation (HD), cold pressing, enfleurage, solvent extraction, and simultaneous distillation exerting low extraction efficiency, great thermal decomposition or hydrolysis of unsaturated ester compounds, and the possible residual organic solvents in essential oils [88]. On the other hand, green approaches were developed to optimize the process in the extraction of essential oils. The supercritical carbon dioxide extraction of *Dendranthema indicum* combined with the molecular distillation performed by Guo et al., 2022, provided an extraction yield of 9.37% at the condition of 750 W of microwave power, 40°C of extraction temperature, 26 MPa of extraction pressure, and 105 min of extraction time [88].

2.4. Selection of the solvent in green chemistry

When selecting a solvent for extraction, the properties as solvent power, boiling point, reactivity, viscosity, recovery, vapor pressure, safety, toxicity, and cost should be considered. Moreover, in the future shift toward green chemistry, the choice of solvent should be in line with the chemical nature of the selected compounds but also the evaluation of the environmental impact and their safe use in nutraceutical formulation. Generally, the dielectric properties of the solvent should match the solubility of desired molecules. Non-polar solvents are usually characterized by low dielectric constants, while polar solvents are widely used due to high dielectric constants. In traditional procedures, polar solvents such as water, ethyl acetate, and alcohols such as ethanol, and methanol, are used for the extraction of hydrophilic components in plants, whereas hexane, ether, and petroleum ether are commonly preferred as non-polar solvents for the extraction of lipophilic secondary metabolites [6]. Despite the discussed chemical behaviour, the condition of operating pressure and temperature should also drive the choice of the appropriate solvents affecting the thermal degradation of compounds and the technical limit of the extraction techniques. For instance, in microwave extraction (MAE) the direct heating of microwave-absorbing plant matrix can be applied to extract thermos-sensitive compounds, releasing target compounds to the colder non-polar solvent in the surrounding matrix. In the case of compounds that are not damaged by high temperatures, polar solvents or hydroalcoholic mixtures can be the best choice despite their higher boiling point.

Beyond the organic solvents commonly used for extraction, growing attention is focusing on natural deep eutectic solvents (NADES). Due to the possibility of a large set of interactions between natural substances acting H-bonding, the modulable physiochemical properties, and combination with innovative extraction techniques NADES are particularly used in green extraction and analysis of botanicals to replace conventional organic solvents [89,90]. Generally, NADES are particularly mixtures of primary metabolites, such as organic acids, amino acids, and sugars sometime the addition of water is recommended to modify the properties of those mixtures. A case study is provided by a flower long used in cosmetics: *Calendula officinalis* L. A comparison of flower extraction efficiency between NADES mixtures and conventional solvents was provided. Considering the bioactive phytochemicals and individual solvent polarity, water and ethanol alone delivered poor extraction performance while higher amounts of both phenolic acids and flavonoids from *Calendula officinalis* flowers were extracted with the studied NADES. Each of tested NADES mixture showed an extraction efficiency toward phenolic acids equal or higher than that of the best conventional solvents [91].

2.4.1. Green techniques and solvent combination in botanicals

This review highlights, by a deep descriptions of case studies, that a combination of green technologies and solvents can increase the bioactives extraction yield by facilitating synergistic mechanism (i.e. mass transfer, cell rupture, solute-solvent interaction) and, at the same time, encouraging the elimination of the hazardous chemicals in the future view of replacement with less toxic solvents that save time loss, environment, and health. Water is the safer extraction solvent with biological compatibility but the capacity in the extraction of plant bioactives is very limited. Despite its behaviour, the conditions of temperatures and pressure in subcritical water extraction (SWE) shifted water polarity towards less polar organic solvents and potentially increased extraction yield of compounds with intermediate polarity [92]. Maravìc et al., 2022 described the phenolic profile of sugar beet leaves extracts (*Beta vulgaris* L.) and related antioxidant capacity largely depended on the applied extraction technique and the solvents. Vitexin revealed the most abundant phenolic compound present in all extracts. The comparison between antioxidant capacity of the extracts was investigated through DPPH, FRAP and ABTS, indicating the lowest antioxidant activity of extracts obtained by solid/liquid extraction compared to other extraction techniques. In particular, the effect of water in the SWE technique revealed a higher efficiency in the higher tested temperature of 150 °C when 6 g of sample is subjected to the SWE at the conditions of 1:20 (m/v) solid-to-liquid ratio, 2 cycles, 50% rinse, water as solvent, 10 min dynamic extraction time [92].

Ultrasounds is the more versatile mean to manipulate any complex mixture characterized by high viscosity and density. This is the case of NADES, mixtures of solid powders concentrated in few amount of water, and sometimes water is absent. NADES allows a proper affinity with non-polar or low-polar compounds but their contact with matrix is hindered by physical behaviour. Stupar et al., 2021 developed efficient method for β-carotene extraction by using sustainable NADES combined with ultrasound assisted extraction to intensify of the extraction process and increase the recovery of β-carotene from pumpkin (*Cucurbita maxima*). In detail, combining the UAE and fatty acid based NADES (Table 2), the extraction process was intensified and resulted in extract rich in β-carotene content recovered from pumpkin. The best NADES can be rated according to the fatty acid ratio C8:C10 (3:1) reaching extraction efficiencies higher than 90 μg β-carotene/mL, higher than other tested composition at C8:C10 (2:1) and M:C10 (2:1) [93]. Generally, pressurized techniques are chosen for controllable applications as a strategy to the recovery of unstable natural compounds. Mesquita et al., 2023., developed of a platform based on the pressurized liquid extraction coupled in-line with a solid-phase extraction step (PLE-SPE) combined with the e use of NADES eutectic mixtures for the recovery of anthocyanins and other phenolic compounds from Jabuticaba (*Plinia cauliflora*), commonly known as Brazilian berry [94]. The success of the overall downstream process was proved by the high extraction efficiency and the purity level of the anthocyanins obtained. Details of the PLE-SPE extraction process were designed with the eutectic solvent composed of choline chloride: lactic acid (1:2 ratio). The optimal operational conditions were selected with a temperature of 90.2 °C and a static time of 12.5 min. Using a commercial C18 adsorbent material, a solid phase extraction system was coupled with the solid–liquid extraction system at high pressure. More than 90% of the total amount of extracted anthocyanins are recovered after 40 min of extraction with NADES system, higher than the relative amounts of water, EtOH 100% v/v, and EtOH 50% v/v at 32.8%, 18.9%, and 38.97% respectively used [94]. Several combinations and related conditions for the extraction of target compounds by using a “green technique-solvent approach” commonly described in literature for botanicals are ranked in the following Table 2.

3. Rational optimization of extraction variables

3.1. One-variable-at-a-time vs. design of experiments

Nowadays, the existence of increasingly complex extraction techniques, with numerous variables capable of influencing the efficiency of the process, also requires the use of appropriate experimental designs. These latter calculations define the independent variables (factors) capable of influencing the process and evaluate their effects on the response variables (dependent variables) that one wishes to control for the extraction or analysis of the compounds of interest [104–106]. It is

possible to maximise the efficiency of the extraction process by combining innovative unconventional extraction techniques with an appropriate experimental design. This is particularly important when the starting matrix is of plant origin and therefore rich in natural compounds. The use of experimental designs can ensure greater extractive selectivity and greater recovery of functional ingredients. Experimental designs can also reduce the number of experiments required, thereby reducing cost, time and environmental impact [97].

The development of an appropriate experimental design plays a key role in experimentation; the presence of errors, especially in the initial stages of the study, can lead to unreliable results and erroneous conclusions. For this reason, experimental design methods are becoming increasingly popular. In the past, the most popular experimental design method was the OVAT approach, which is still popular today because of its simplicity. However, in this approach, only one factor is changed at a time, while all the others are held constant at their nominal values, which prevents the influence of factor interactions in the process from being evaluated [107]. The main problem with OVAT is therefore the presence of a small experimental matrix with a small range of independent variable settings. It also requires a large number of experiments for process optimization [104–106]. Therefore, we can only define this approach as suitable for the optimization of simple experimental processes with one or two independent variables. It is therefore not suitable for the optimization of green techniques such as SFE or PLE, which have many process variables and the risk of producing incomplete or incorrect results. For these mining techniques, experimental optimization by multivariate analysis is more appropriate [108]. This approach allows all interactions between factors to be evaluated simultaneously at several levels, and the results obtained represent the average value of the entire experimental domain. This makes it possible to select the best process conditions even beyond the experiments performed, thus having more precise and reliable results than OVAT [104].

3.2. Design of experiment (DoE)

In order to evaluate the influence of each factor and to find the optimal settings, methods based on the multivariate design of experiments (DoE) focus on modelling and statistical analysis to define the factors that have a significant impact on the process. The correct planning of an experimental design is a fundamental step in obtaining reliable data capable of validating the experimental hypotheses. First of all, it is necessary to evaluate the independent variables, i.e. those factors that are considered capable of influencing the experimental process. The independent variables must be easy to control and vary according to the extraction technique under consideration. In particular, the most important factors for microwave extraction are extraction time, solvent composition, temperature and drug: solvent ratio [97]. On the other hand, the factors that influence the process are temperature, pressure, solvent composition and extraction time for the PLE technique [100]. The SFE-CO_2 technique is more influenced by pressure, temperature, and co-solvent type [100,109] and finally, for the ultrasound technique, the main factors are temperature, pressure, solvent composition, wave frequency and extraction time [97,110]. Each of these factors is expressed in levels ranging from −1 (minimum) to 1 (maximum) with 0 being the central value [111]. Finally, the third key element of an experimental design is the dependent variables, which represent the response variables that we want to define at the end of the experimental design, such as maximizing the recovery of specific bioactive molecules from plant matrices.

There are numerous applications of the DoE in different fields, certainly today there is a growing interest in its use in the omics-science, both for targeted studies (where a group of defined metabolites is controlled) and non-targeted (where all metabolites of a sample are controlled) [112]. However, it is important to limit the number of factors and levels in the experimental design, as this will determine the number of experiments to be carried out to optimize the extraction process, and for this reason different models for multivariate analysis are currently available. In particular, we can distinguish between methods for the preliminary evaluation of the factors to be considered and methods for the optimization of the response [97,112,113].

3.2.1. Preliminary factors screening

One possible application of factor designs involves their application for the initial screening of factors. In this context, the most popular part is the factorial design. This model has several variants.

- Full Factorial Design (2^k): in this model 2 represents number of levels and k is the number of factors investigated. Indicated for non-continuous variables. It allows the effects and significance of each factor and their interactions to be defined. However, it is not suitable if the number of factors investigated is too high ($k > 2$) [114,115].
- Fractional factorial design (2^{k-n}): this model is applicable when FFD would result in too large a number of experiments or if it is suspected that the interactions between factors are negligible. In fact, FFD provides information on the significance of the independent variables but not on their interactions, the effects of the main factors being confused with those of the interactions between factors [116].
- Plackett-Burman design: this is a very simple method that can be used for factor screening. It is often selected precisely because of its simplicity, which allows a small number of experiments to be performed. Also, in this case, factor interactions are not evaluated. Economical and efficient option for assessing the robustness of the data [117,118].

3.2.2. Optimization of extraction conditions

They are based on quadratic models that allow for extremes defined as maximum and minimum representing critical conditions. This approach is fundamental to allow the optimization of conditions.

- Central Composite Design (CCD): has a full or fractional 2-level factorial design (which has an advantage because it can also be run as a screening), a central pento, and two axial points. The disadvantage of this approach is the application of experiments with all factors at positive and negative levels with the risk that runs with extreme conditions that may give misleading results [119,120].
- The Doehlert matrix: is an economical, versatile and efficient approach to modelling experimental data. An important feature of this design is the possibility of studying different variables and different numbers of levels of the same matrix, making it particularly suitable for studies in which one variable is considered more closely on a different number of levels. Finally, it requires a reduced number of experimental points, thus being very efficient and economical compared to other models such as the CCD and Box-Behnken design [121].
- The 3-level factor design: this approach requires a high number of experiments to obtain a quadratic model and involves experiments with all positive and negative factors. It cannot be applied with $k > 2$ [112].
- Box-Behnken design: Originated in the 1960s as a modification of the 3-level factorial plan in which a factor must necessarily be maintained at its mean value (zero point) in every experiment. In addition, this model also includes at least one experiment in which all factors are at the “zero” value, called center points. Increasing the number of center points in an experimental design using the Box-Behnken approach makes it possible to increase the degrees of freedom, namely the accuracy of the data obtained by being able to highlight any anomalies during the execution of the experimental design [122–124].

4. Conclusion and future perspectives

Given the nutritional and therapeutic role of natural bioactive

components, plants metabolites have numerous applications in nutraceutical and cosmetic industry. Among the rising diffused plant-based products, botanicals are health promoting products with increasing interest in market. The recovery of bioactive components from plants and their by-products is related to extraction process provided by a balance between the performance of extraction techniques and the solvents used as mass transfer media from the matrix. This review provides a critical insight into current green extraction procedure in the natural product chemistry. Its purpose was to provide updating on strategies for improving both extraction efficiency and eco-sustainability.

Nowadays, the main challenge in analytical chemistry is to include environmental considerations in the design and optimization of the analytical processes, in order to develop more sustainable procedures. In the last decades, several innovative technologies were developed in fields of extraction processes and are commonly considered as green extraction processes, such as MAE, UAE, SFE-CO_2, PLE and PEFE, as they are characterized by low consumption of organic solvent, analysis time and energy, compared to classical extraction techniques.

Generally, an analytical procedure is defined as "green" without a real assessment of their environmental impact through accredited tools. Over the years, several metric platforms have been developed for the qualitative and quantitative greenness evaluation of analytical processes. Most of the traditionally employed metric tools are generic and inadequate for the greenness evaluation of all the steps of an analytical process. Therefore, specific metric tools are need for crucial steps of analytical process.

In the chemistry of natural products, the extraction procedure is a fundamental step and is the one most impacting the eco-sustainability. To date, there are no specific metrics for the extraction phase and one of the future prospects could be to develop a specific platform in the direction of green improvement of the procedure.

In GAC, in addition to the qualitative and quantitative assessment of the environmental impact of the analytical process, it is essential to minimize it. Thus, it is necessary to identify the parameters responsible for the environmental impact of the extraction phase and optimize them in order to increase the eco-sustainability of the analytical process. The main factors related to the environmental risk of a process are the reagents, the waste generated, and the energy used. The parameters to be monitored and optimized in the advanced extraction techniques are numerous. With the aim to combine all the parameters a DoE is required to understand the effects of multidimensional and interactions of input factors on the output responses of extraction phase. Therefore, future research priorities in this area should focus on building and managing a DoE considering the eco-sustainability of the analytical process as additional parameter for a totally green workflow in the domain of the botanicals.

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CRediT authorship contribution statement

Ciro Cannavacciuolo: Writing – original draft, Conceptualization. **Stefania Pagliari:** Writing – review & editing, Writing – original draft. **Rita Celano:** Writing – original draft. **Luca Campone:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Luca Rastrelli:** Writing – original draft, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

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

Data availability

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

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