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Review Article

Sustainable extraction bioactive compounds procedures in medicinal plants based on the principles of green analytical chemistry: A review

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ABSTRACT

This review article points out, through an overview, aspects that are related to the procedures established by green analytical chemistry, for the extraction of bioactive compounds in plants, through the use of assisted techniques, as well as green solvents. Procedures that have less negative impact on the environment are being increasingly required for the extraction of biocompounds in the area of analytical chemistry due to aspects of sustainability, profitability and efficiency. To this end, green procedures aim to design environmentally benign chemical processes and synthetic methodologies, to eliminate or reduce the use of dangerous and toxic chemicals at any stage of production in industry or even in the laboratory. These extraction procedures will be defined as "green", when using alternative solvents, reducing energy consumption, in addition to ensuring the safety and high quality of the extract. This review provides an overview of the green procedures applied and which had an effective action in the extraction of bioactive compounds in medicinal plants, supported thus by innovative, sustainable, and unconventional energy sources.

1. Introduction

In the last decade, "green" extraction techniques, have gained attention considering that they encourage the elimination of toxic substances and volatile organic solvents [1].

According to Paiva *et al.,* [2], environmentally friendly analytical methods appear in a scenario where significant improvements are being sought for the development of sustainable, profitable, and truly efficient techniques. Conventional organic solvents such as hexane, ethyl acetate, chloroform, acetone, or methanol, among others, are widely used to carry out the extraction process, due to its dissolution capacity and extraction power.

Although many engineering and process management approaches seek to minimize waste or achieve greater energy efficiency, green chemistry look for more deeply goals, optimizing each step of a process. For this purose, twelve principles have been proposed. Avoid waste; atom economy; less dangerous chemical synthesis; projection of safer chemicals; safer solvents; energy efficiency project; renewable raw materials; reduce derivatives; catalysis; degradation project /end of life project; real-time monitoring and control of processes and inherently safer chemistry [3].

Two of the twelve principles of green chemistry concern the use of solvents and safer reaction conditions, and waste prevention. The toxic and volatile nature of many organic solvents, particularly chlorinated hydrocarbons, commonly used in large quantities for organic reactions, created an alert to human health and the environment [4,5].

As the development of ecological methods is cheaper than cleaning the polluted environment, ecological analytical methodologies must be made very attractive from an aesthetic and economic point of view [5,6].

As such, the extraction techniques are defined as "green", if alternative solvents are used, reducing energy consumption, in addition to

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ensuring the safety (Fig. 1) and high quality of the medicinal plant extract [7].

For an effective extraction according to the principles of green chemistry, the correct selection of ecological green solvent is always a challenging task (ARAIN, 2016), considering that other factors also influence the extraction process, among which, the plant matrix [8].

In this article, we will discuss the methods of extracting bioactive phenolic compounds (Fig. 2) from medicinal species that are considered more ecological, as well as the results of research that have been developed over the past ten years.

Plants and humans have a complex relationship extending far back into the start of humankind. Today plants are useful to provide nutrition for people and animals across the globe as well as represent a rich source of fiber and bioactive compounds for pharmaceuticals and agro-industrial products.

Medicinal plants are those that have therapeutic potential to prevent and/or treat diseases. Its use in the formulation of medicines and commercial chemicals gained momentum with the development of organic chemistry, from the 19th century. According to WHO, currently, about 60% of the world population and 80% of the population in developing countries, use medicinal plants to treat health through traditional medicine [9,10].

Medicinal plants (whole plants or specific parts) have been used in several countries around the world, as they are important sources of bioactive compounds [11,12], also known as phytochemicals. These compounds are precursors for the synthesis of natural and synthetic medicines, cosmetics, and food supplements [12-14]. They are synthesized by the secondary metabolism of the plant, due to their vulnerability to abiotic and biotic factors adverse to the environment in which it is inserted, protecting its survival [10,14,15].

In this way, bioactive function as insect attractants, pollinators, and seed dispersants; promote protection against herbivory; stimulate the formation of root nodules; act as UV-B screening compounds, such as phytoalexins, signaling compounds, growth hormones [16] and as toxic and/or potentially toxic metal chelators [10]. In addition to these functions, bioactive compounds also contribute to the sensory properties of the plant, such as color [13], also giving flavor to drinks [17], such as wines, teas, and juices; and functional (biological) properties, among which, antioxidant activity [18-20], antidiabetic, anticancer [13], antibacterial [21,22], anti-hyperglycemia, anti-hypertension [23].

The composition and concentration of bioactive compounds in medicinal plants are indicators of quality, and add value to them [24]. Some factors influence the quality and quantity of bioactive synthesized by these species [9], among which, environmental factors such as water stress [17], thermal, saline [25], UV-B radiation [26], temperature, excess or lack of nutrients in the soil and presence of toxic metals [10], as well as physiological conditions and biological characteristics of the plant [10,24].

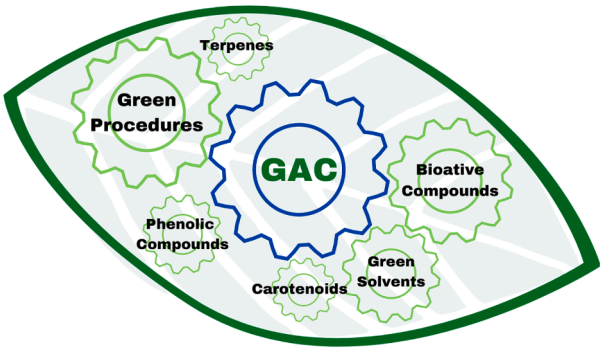

Fig. 1. Extraction bioactive compounds according to Green Analytical Chemistry (GAC); (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The secondary metabolites produced by medicinal plants are divided into three groups: terpenoids, nitrogen compounds, and phenolic compounds [10]. Among these, the phenolic compounds constitute one of the main groups present in medicinal plants [13], they are formed by more than one hydroxyl group, being the methylated or glycosylated and; its biosynthesis takes place in two ways, via shikimic acid (responsible for most of it) and malonic acid [10].

Several works describe the identification and determination of bioactive phenolic compounds present in different medicinal plants [19,27-31].

Although it is known that medicinal plants have a range of bioactive compounds, it is estimated that these compounds have been little explored [11], which has aroused greater interest in the study of biological and photochemical potential, on the part of the scientific community, food, pharmaceutical, and cosmetic industries.

The starting point for using, quantifying, and identifying these compounds is plant extraction, which constitutes the most important phase in these processes [32]. In the last few years, several methods have been developed for the extraction of bioactive compounds present in medicinal plants. In Fig. 3, are shown the results of an investigation involving phenolic compounds, extraction methods in medicinal plants. It is possible to observe that in the last ten years there has been a significant increase in the number of works involving procedures for the extraction of bioactive compounds in medicinal plants.

Currently, there is a growing concern of the scientific community to develop environmentally sustainable methods for the extraction of bioactive compounds [33], since these methods reduce or eliminate the use of organic solvents harmful to the environment, contributing to the safety, quality, and applicability of plant extracts [11].

2. Green techniques for extraction of bioactive compounds

In the last decades, the improvement of the pharmaceutical industry has guided the rapid evolution of different methods for the extraction and separation of bioactive compounds. Bioactive compounds from biological resources are expected to play a vital role as an essential resource in the promotion of food additives and new medicines. Thus, quickly attracting increasing attention among researchers [34].

It is important to pay attention to the food sector, as fruits and vegetables are fundamental to human health. Since they provide different flavors and are associated with improving the quality of life. The consumption of vegetables and fruits is inversely associated with the development of cardiovascular diseases and tends to be associated with protection against the main chronic diseases related to diet [35].

In vegetables, components related to protection are activated when they are under some kind of adversity. These compounds are directed from the secondary metabolism of plants and are presented as phenolic compounds, carotenoids, vitamins, among others. Bioactive compounds are found in foods of natural origin or can be produced synthetically. They have specific metabolic or physiological actions, provided their safety for human consumption is proven [36].

According to Lin & Tang [37], the wide range of polarity and physical properties of natural compounds makes it difficult to extract metabolites. For a long time, water, hexane, acetone, alcohol, chloroform, and ethyl acetate have been used to extract phenolic compounds from some varieties of fruits and medicinal plants. However, these solvents are not highly recommended for working with separation on a more comprehensive scale, due to their substantial deleterious effect, and consequently, the low extraction capacity [38].

Thus, there has been a growing demand for the substitution of toxic solvents with solvents considered more ecological and that enhance extraction. There is an increasing number of researches on the extraction and separation of bioactive compounds in medicinal plants and fruits, such as flavonoids, catechins, phenolic acids, terpenoids, and saponins.

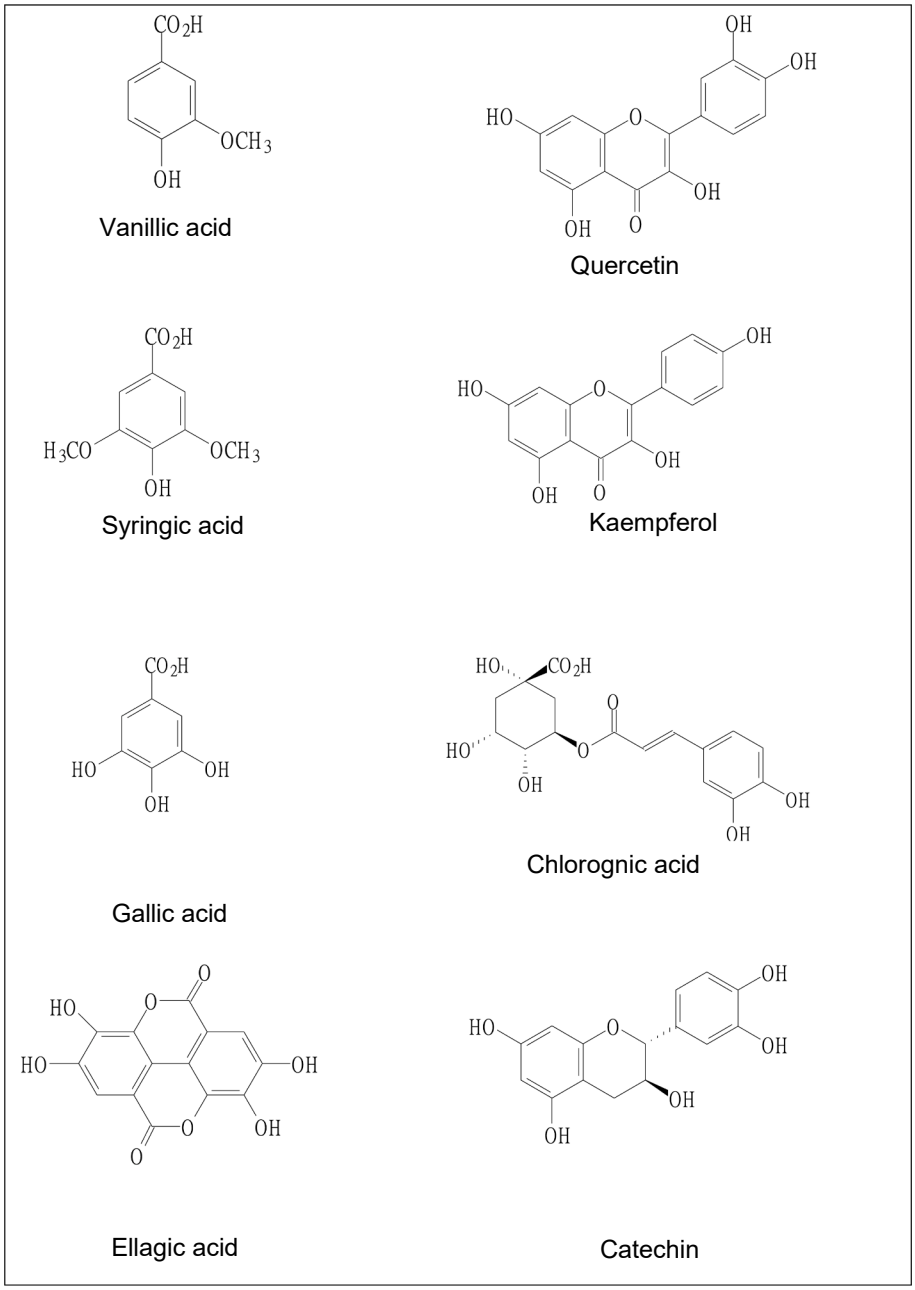

Fig. 2. Chemical structure of the bioative phenolic compounds.

3. Conventional and modern extraction methods

Considerable effort has been made by the researchers to find extraction methods to obtain high efficiency and effectiveness. Where, efficiency refers to the extraction yield, while efficiency refers to the potency (magnitude of bioactivity /ability to produce an effect) of the extract.

The extraction methods can be classified main in conventional and non-conventional or modern methods. The conventional extraction methods require the use of organic solvents toxics, long agitation time and high temperature (e.g. maceration and distillation). Modern extraction methods, are procedure that reduced the use of toxic organic solvent and extraction time (e.g. microwave and ultrasound assisted extraction techniques). On the other hand, most sustainable approaches for the isolation or extraction of biological compounds in plant [39]

In order to obtain better quality and high efficiency of herb extraction, it is necessary to optimize methods. Analytical procedures have several critical steps such as sampling, sample preparation, quantification, statistical evaluations, etc [40,41].

The need to select the most appropriate extraction methodology is evident from the fact that when different methods are applied to the same plant material with the same solvent, the extraction efficiency can vary significantly. The method selected as the most appropriate also needs to be standardized to achieve an acceptable degree of reproducibility [42].

It is important to note that the choice of the appropriate solvent is of the utmost importance, along with the application of a compatible extraction method. Polar solvents extract polar substances, and non-polar material is extracted by non-polar solvents. Extraction by non-polar solvents is the most popular method of extraction [43].

According to Huie [44], generally, the mixture of hydroalcoholic solvents (a mixture of alcohol and water in varying proportions) produces high extraction yields, due to their expanded polarity range. Sample preparation is the crucial first step in the analysis of plant

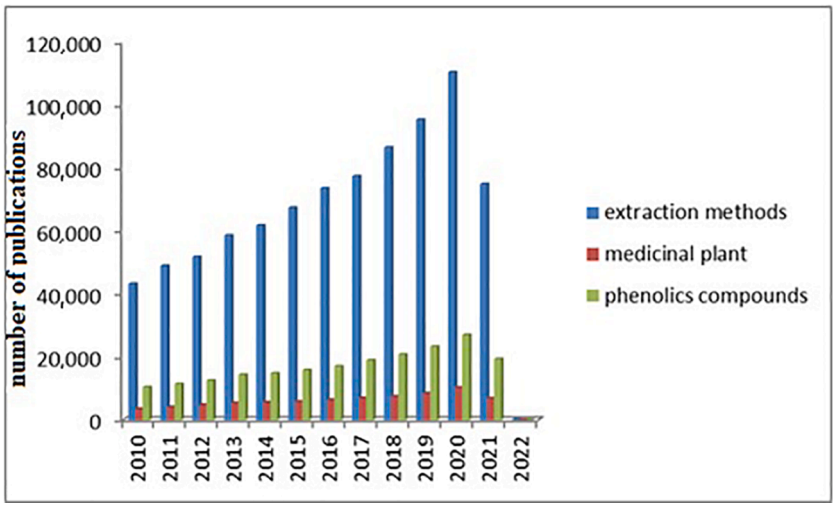

Fig. 3. Publications using the keywords: extraction methods; medicinal plant; phenolics compounds, among 2010 and May 17, 2021. Science Direct access platform.

compounds, as it is necessary to extract desired chemical components from the plant-based material for further separation and characterization.

In this broad-spectrum, it is important to indicate that, in many cases, analytical strategies depend on the automation of sample preparation methods. In the analytical procedure, sample preparation is considered the most important part of the process, because of the precision and accuracy of the method, depending on this indication [45].

The main objectives of the sample preparation stage are to purify, extract, and enrich the analytes and, eventually, modify the sample to adapt it to the requirements of the analytical apparatus. In some cases, isolation and sample enrichment steps are necessary, as only a small number of techniques are sensitive enough to directly determine a particular type of analytical response [46].

More than 80% of the analysis time is spent on collecting and preparing samples, so sample preparation is a critical part of the analytical process. Often, the sample preparation step is based on the extraction process [47].

For extraction of therapeutically desired active constituents, various solvents such as water, ethanol, methanol, etc. are commonly used. Sometimes, solvent mixtures are also used to obtain better extraction efficiency. The development of modern sample preparation techniques has significant advantages over conventional methods in terms of reducing the consumption of organic solvent and minimizing sample degradation. They also result in the elimination of undesirable and insoluble components of the extract [42], producing higher quality extracts [48]. Due to these advantages, the number of researches related to the extraction of the bioactive compounds through non-conventional extraction processes has been growing in the last ten years, considered ecologically correct, such as extraction assisted by microwave and ultrasound, about the method of maceration taken as conventional. In Fig. 4, these data are presented.

Until 2015, the SFE techniques present the highest results in relation to the others, but it is possible to observe that after this period other extraction techniques increased the application levels, with the main highlights being the MAE and UAE techniques. This indicates that the usability of such techniques over the years (Fig. 4), directs to use and indicative of greater efficiency to other techniques.

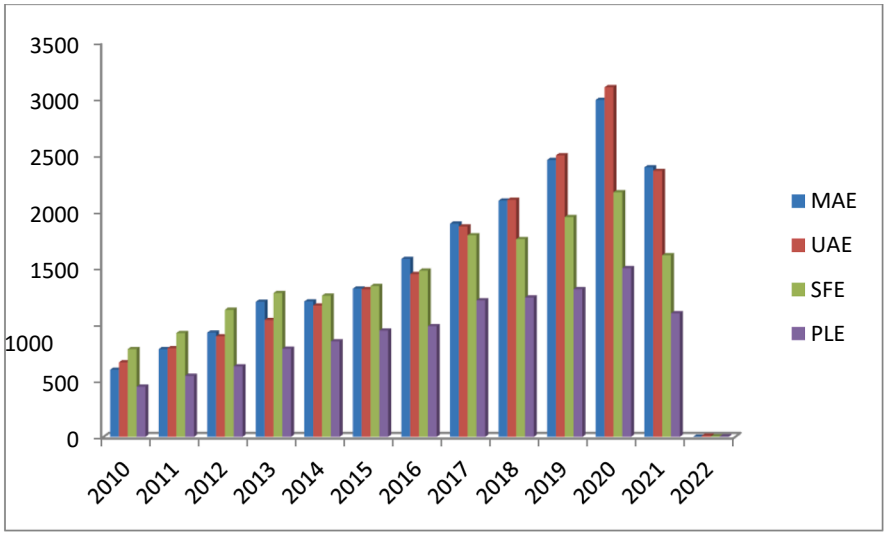

Fig. 4. Publications using the keywords: microwave assisted extraction (MAE); ultrasound assisted extraction (UAE); supercritical fluid extraction (SFE) e pressurized fluid extraction (PLE), among 2010 and May 17, 2021 (Science Direct).

The field of application of different types of extraction techniques is constantly increasing. Modern methods include microwave-assisted extraction (MAE), ultrasound-assisted extraction (UAE), supercritical fluid extraction (SFE), solid-phase microextraction (SPME). The literature indicates that they are widely used in a variety of applications, such as separations in analytical chemistry, industrial processes in hydrometallurgy, food engineering, pharmaceuticals, and waste treatment [49].

According to Kothari *et al.,* [40], classic methods are quite simple and continue to have wide use, but they can also be insufficient and slow, in addition to consuming large amounts of organic solvents and causing degradation of heat-labile constituents. In the use of conventional methods, it is possible to observe problems related to the lack of consistency, safety, and effectiveness. It is worth mentioning that, when using more modern processes, it is possible to observe the elimination of additional steps of cleaning and concentration of the sample before the chromatographic analysis, for example. In addition to improvements in extraction efficiency, selectivity, reduction of time spent associated with a higher yield of extracted compounds. These results are shown in Table 1.

To overcome the main deficiencies contained in the more conventional extraction methods, mainly associated with the use of high temperatures and prolonged extraction times, with techniques that have low efficiency, and that besides causing degradation of thermolabile polysaccharides, they end up causing numerous other serious consequences. Faced with reality, more advanced techniques for extracting compounds were proposed in the scientific community. Extraction techniques such as; Ultrasound-Assisted Extraction (UAE); Microwave-Assisted Extraction (MAE); Pressurized Fluid Extraction (PLE) and Supercritical Fluid Extraction (SFE), high-speed homogenization extraction (HSH), electric field pulse assisted extraction (PEF), have emerged in recent decades to improve green extraction of bioactive carbohydrates [50].

3.1. Ultrasound-Assisted extraction (UAE)

Another modern assisted extraction technique is the one established through the use of ultrasound (UAE). The literature shows that this technique was introduced in the year 1950 for brewing from hops. Since then, several applications for this type of technique have been registered, mainly when dealing with different types of secondary metabolites from a variety of plant samples, analyzed and extracted efficiently [51].

Ultrasound is a key technology to achieve the sustainable goals of green chemistry. Complete extractions of various components (flavors, pigments, antioxidants, and other organic and mineral compounds) from different matrices (microalgae, foods, yeasts, and plant materials) in a short time are achieved with high reproducibility, reduced solvent consumption, and purity of the final product. According to Qiao *et al.,* [52] ultrasound-assisted extraction has been widely applied in the extraction of phenolic acids due to the high efficiency of the method.

According to Vinatoru *et al.,* [51], the UAE uses ultrasonic energy (greater than20 kHz) for extraction using an ultrasonic bath and/or ultrasonic probe. According to Suslick *et al.,* [53], the effects produced by ultrasound are attributed to the formation, growth of the collapse of bubbles of gases dissolved in the liquid from the compression and decompression of molecules that constitute the medium. More specifically, when using the ultrasound-assisted extraction technique on plant material, the suspended powder sample induces the asymmetric collapse of the bubbles, resulting in a more efficient extraction.

The type of pre-treatment used in the study sample will also contribute to the performance of the extraction. The UAE has been extensively investigated for its efficiency in applying natural products. Allowing extraction at lower temperatures than normally used, reducing solvent volumes, in addition to improving extraction and purity [54,55].

According to Armenta *et al.,* [56], "green" extraction techniques are important alternatives to the classic procedures with greater harmful

Table 1
Comparison of the yield of bioactive compounds in different plant species and fruits, using conventional extraction method maceration and assisted extraction method.

		conventional	method		Assisted	method		
Vegetable material	Time and temperature	Mass/ solvent	Yield	Time and Temperature	Mass/ solvent	Method	Yield	Reference
Psidium cattleianum Sabine	120 min., 40 °C	1 g/ 10 mL of 90% ethanol	121.81 mg[a] 477.54 mg[b] 351.80 mg[c]	90 min., 40 °C	1 g/ 10 mL of 90% ethanol	US	125,88 mg[1] 589,49 mg[2] 374,05 mg[3]	[168]
Olea europeae L.	24 h., at room temperature	0,5 g/ 25 mL of 70% ethanol	57.28 mg[b]	3 min., 86 °C	0,5 g/ 25 mL of 70% water	MW	104.22 mg[2]	[169]
Clitoria ternatea G.	150 min., 50 °C	1 g/ 15 mL of water	72.00 mg[b] 25.00 mg[d]	150 min., 50 °C	1 g/ 15 mL of water	US	87.00 mg[2] 29.00 mg[4]	[170]
Labisia pumila	2 h., 90 °C	1 g / 20 mL of 10% ethanol	0.08 mg[b]	10 min., at room temperature	1 g / 20 mL of 10% ethanol	US	0,11 mg[2]	[171]
Cassia alata	2 h., 60 °C	1 g/ 20 mL of 100% ethanol	20.68 mg[b] 70.13 mg[d] 12.01 mg [f]	4 min., 40 w/ mL of power	1 g/ 20 mL of 100% ethanol	MW	37.92 mg[2] 135.18 mg[4] 17.67 mg [6]	[172]
Citrus reticulate L.	20 h, 40 °C	1 g/ 15 mL of 80% methanol	28.40 mg[b]	60 min., 45 °C	1 g/ 20 mL of 80% methanol	US	32.48 mg[2]	[173]
Arbutus unedo L.	93.2 min., 79,6°C	50 g/ L of 23.1 % ethanol	1.38 mg g[-1c]	42.2 min., 131.1 °C	50 g/ L of 12.1 % ethanol	MW	1.70 mg/ g[3]	[174]
Juglans regia L.	112.5 min., 61.3 °C	140 g / L of 50.4% ethanol	124 mg[e] 53.3 mg[d]	3.0 min., 107.5 °C	140 g / L of 67.9% ethanol	MW	194.9 mg[5] 66 mg[4]	[175]
Thymus serpyllum L.	60 min., 80 °C	1:30 mL of 50% ethanol	26.6 mg[b] 14.3 mg[c]	15 min. 25 °C	1:30 mL of 50% ethanol	US	32.7 mg[2] 16.7 mg[3]	[176]

[a] Eq. mg of cyanidin-3-glycoside/100 g of peel; [b] Eq. mg of galic acid equivalent; [c] mg of Catequin; [d] mg of Quercetin; [e] mg de Eq. Clorogenic acid; [f] mg of Kaempferol.

effects used in the past and their study seeks to improve the sensitivity and selectivity of analytical methods. The authors point out that the sample preparation step involving the use of microwaves and ultrasound favors the development of fast and safe methodologies, especially for dissolving and digesting samples.

Aryanti *et al.,* [57] evaluated the presence of anthocyanins in rosemary (Hibiscus sabdariffa L.) extracted by the conventional maceration method (for 24 h) and by the ultrasound-assisted process (frequency of 40 kHz for 40 min) at room temperature). The effects of the types of solvent (water and ethanol) and the solute/solvent ratio of the extractions were studied (1:10 and 1:5 m/v). Comparing the methods, the authors concluded that ultrasound-assisted extraction using the 1:10 solvent solute ratio is more efficient than maceration and that water is the best solvent in the evaluated extraction processes. the result found by the authors can be explained by the fact of anthocyanins, pigments responsible for coloring plants and fruits, are dependent on the pH and water-soluble.

Sousa et al., [58] developed and optimized an ultrasonic bath extraction method for phenolic compounds in Croton heliotropiifolius leaves. The Doehlert Matrix was used to optimize the factors composition of solvents (37.5% v/v of ethanol), the volume of extractor solvent (11.4 mL), temperature (54.8 °C), and time of extraction (39.5 min). The bioactive compounds identified in the extract by HPLC DAD were catechin, quercetin and gallic, vanillic, ellagic, *trans*-cinnamic, *p*-coumaric, syringic, ferulic, and chlorogenic acids. The method developed is efficient, fast, simple, and considers the principles of green chemistry.

Moreira and Dias [29], developed and optimized a method of ultrasound-assisted extraction of phenolic compounds (25.0 to 32.5 μg g^{-1} of caffeic acid, 75.6 to 88.2 μg g^{-1} of rutin, 15.5 to 22.5 μg g^{-1} of catechin, and 23.5 to 110.7 μg g^{-1} of *trans*-cinnamic acid) in *Physalis angulata*. The compounds were determined by HPLC DAD and the Doehlert Matrix was used as a tool to optimize the variables extractor solvent composition (15 mL of the mixture 57% water, 35% ethanol, and 8% methanol) and sonication time (10 min).

In a Review paper the effects of UAE parameters on the yield, composition and antioxidant, anticancer, and antimicrobial properties of polyphenol extracts were presented by Dzah *et al.,* [59] The result of the work showed that extraction temperatures above 50 °C degrade the polyphenols in the extracts, lower frequencies in the ultrasound power range below 40 kHz are more effective, the polyphenol yield increases with increasing power up to a limit and the greater power of ultrasound produces hydroxyl radicals, which are degrading agents of polyphenols.

Kaltsa *et al.,* [60] developed a green method of extracting polyphenolic substances present in elderberry flowers (Sambucus nigra), a plant is known for its important bioactivity, using a natural eutectic solvent and a pre-treatment step assisted by ultrasound (at a frequency of 550 Hz and a power of 50 W). The extraction factors optimized from the response surface methodology were: eutectic solvent concentration (85% m/v), solid–liquid ratio (60 mL/g) vegetable mass/solvent), and agitation speed (200 revolutions per minute). The authors highlight the importance of using ultrasound, since there was an increase in the recovery of polyphenols, in addition to being a safe, low-cost, and reproducible technique.

Sendi *et al.,* [61] optimized a method of ultrasound-assisted extraction of flavonoids from the medicinal plant Artemisia herba-Alba. The antiradical activity of the obtained extracts was determined. The optimized factors were solvent concentration (50%), temperature (55 °C), extraction time (50 min) and solvent volume / sample mass ratio (90 mL g^{-1}). The developed method was compared with maceration and soxhlet extractions and advantages such as reduced extraction time and energy consumption, in addition to the quantified amount of flavonoids were confirmed, thus proving the efficiency of the technique.

The effects of ultrasound potency on black cumin seed extract (*Carum carvi* L.) were studied by Shaterabadi *et al.,* [62]. The response surface methodology was used to study the evaluation of the qualitative properties of the obtained extract. Ultrasound-assisted extraction was used since it avoids the excessive use of solvents and reduces the operating time in the extraction processes. The method was compared with the Soxhlet method and two types of sonication were studied: continuous and pulsed, the latter being more effective in extracting the components. The optimal results indicated were: 200 W power, 15 min extraction time, and pulsed sonication (4 s on, 2 s off).

Tungmunnithum *et al.,* [63], optimized and validated ultrasound-assisted extraction of *trans*-rosmarinic acid, a phenolic compound known for its antioxidant and antimicrobial potential, from leaves of *Plectranthus scutellarioides* (L.) R.Br. The factors optimized by the complete factorial design were ultrasound frequency (30 kHz), extraction time (45 min), and solvent concentration (pure ethanol). The developed method is more efficient and faster than the conventional reflux extraction.

Vuong *et al.,* [64], studied and validated experimental conditions for ultrasound-assisted extraction of euphol, a compound with anticancer activity, of *Euphorbia tirucalli* using the response surface methodology tool. Several solvents were tested in an ultrasonic bath to evaluate the most efficient way to extract euphol at room temperature, for 60 min and at a power of 150 W. Box-Behnken planning was employed to optimize the factors of temperature (60 °C), time (75 min), ultrasound power (150 W), and a solvent-to-fresh mass ratio of the sample (100: 32 mL g-1). The proportion of solvent that offered the greatest extraction of the compound was 4: 1 v / v ethyl acetate: ethanol.

3.2. Microwave-Assisted extraction (MAE)

Microwave-assisted extraction (MAE) is a simple, ecological, and economical technique for the extraction of biologically active compounds from different types of plant materials. Its application for this material was first reported by Ganzler, around 1986 [65,66].

Microwave-assisted extraction meets the requirements of green analytical chemistry and has the characteristics of reduced extraction time, energy consumption, use of solvents, and CO_2 emissions. It was developed to isolate compounds with high added value from solid samples [67]. Alupului *et al.,* [68] adds that microwave-assisted extraction has advantages from an economic point of view: low operating cost, simplicity, and efficiency.

Microwaves have electric and magnetic fields perpendicular to each other. The electric field causes heating by two simultaneous mechanisms, namely, dipolar rotation and ionic conduction. Dipolar rotation is due to the alignment in the electric field of molecules that have a dipolar moment in the solvent and the solid sample. For extraction, the advantage for establishing microwave heating is the rupture of weak hydrogen bonds promoted by the dipolar rotation of the molecules [65].

The microwave extraction mechanism occurs in stages: in the first stage, solute desorption occurs from the active sites in the sample matrix under conditions of high pressure and temperature. The second step involves the diffusion of the extraction fluid in the matrix. Then, depending on the sample matrix, the solutes can separate from the matrix in the extraction fluid. The efficiency of MAE can be attributed to: (1) improvement in solubility and mass transfer effects and (2) increased disturbance of surface balance [69]. According to Mandal *et al.,* [70] the factors that influence MAE are: volume and nature of the solvent, extraction time, microwave power, matrix characteristics, and temperature.

According to Li *et al.,* [67], several organic compounds such as essential oils, antioxidant compounds, aromatic compounds, and pigments have been recovered from plant matrices using MAE.

According to Belwal *et al.,* [55], microwave extraction efficiency depends on the nature of the solvent and the sample. The solubility of the different compounds to be extracted can be maximized by fixing the solvent mixture ratio and controlling the temperature/potency ratio. Microwave-assisted extraction has many advantages, including the extraction of volatile compounds (extraction using solvents) and non-volatile compounds (dry extraction). Some works reported in the

literature use microwave energy in a system to obtain essential oils, presenting excellent yields, better oil quality when compared to a conventional distillation system [71,72].

Alupului *et al.,* [68], investigated the influence of parameters in the extraction process of flavonoids, glycosides, and polyphenols from leaves of Cynara scolymus: temperature/microwave power and extraction time and yields. The authors state that in a closed system, the parameters that can affect the extraction efficiency are the sample size, the nature, and volume of solvent, pressure, temperature, microwave power, and extraction time. Approximately 0.4 g of the 0.315 mm diameter plant material was mixed with a solvent. The extraction was carried out in a closed microwave system with a time-varying between 1 and 5 min and a temperature between 70 and 100 °C. The temperature of 70 °C and the time between 3 and 5 min provided the maximum extraction yield of the studied compounds.

Boukroufa *et al.,* [73], optimized a sustainable process with high extraction yields without toxic organic solvents using ultrasound and microwave techniques to extract essential oil, polyphenols, and orange peel pectins. Microwave essential oil extraction was compared with distillation extraction and significant differences between the two methods were not observed. The 500 W power in the microwave was used since in just 15 min the oil was extracted. The water used in the essential oil extraction process was reused for use as a solvent in the extraction of polyphenols and pectins. The polyphenols present in the matrix were obtained by ultrasound-assisted extraction and pectins by microwave-assisted extraction.

Bouras *et al.,* [74], used Box-Behnken design to optimize a microwave extraction method for polyphenols in quercus shells. The effects of the parameters extraction time, microwave power, particle size, solvent composition, and pH were studied. The results obtained were compared with those obtained by conventional solvent extractions at room temperature and reflux at 100 °C. The variables studied that had a significant effect on the process resulted in the following optimal conditions: particle size 0.5x1x0.3 cm3, power of 45 W, the irradiation time of 60 min, pH of 10.75, and solvent composition of 33% ethanol and 0.38% of methanol.

Dahmoune *et al.,* [75], optimized a method of extracting polyphenols from leaves of Myrtus communis using microwaves. The method was compared with ultrasound-assisted extraction and conventional solvent extraction and the authors concluded that the extracts obtained by microwaves showed higher values of tannins, total flavonoids, and antioxidant activity. The optimum parameters were 42% ethanol concentration, microwave power of 500 W, the irradiation time of 62 s, and the solvent / solid ratio 32 mL g-1.

Aslam *et al.,* [76], applied the microwave-assisted extraction technique to extract polyphenols from different parts of the *Ocimum basilicum* plant (seeds, stems, and flowers) using three solvents with different polarities (water, methanol, and ethyl acetate). The method was compared with two classic techniques (reflux and soxhlet extraction). The highest concentrations of polyphenols were obtained from plant stem extracts using the microwave-assisted extraction technique using methanol as the solvent. High efficiency and reduced time and energy consumption are the characteristics that the authors attribute to the applied technique.

Mustapa *et al.,* [77], obtained extracts of *Clinacanthus nutans*, a well-known medicinal plant from Southeast Asia with medical and nutraceutical applications, from a pre-treatment step using from MAE for the determination of polyphenols. Curves were drawn with the data obtained from the extractions and adjusted to two theoretical kinetic models. The result showed that the pre-treatment step using microwaves favored the increase in the extraction yield of the polyphenols and the reduction in the extraction time. The process parameters studied were: ethanol concentration in the solvent mixture, microwave power, and solvent-to-feed ratio.

Nayak *et al.,* [78], evaluated the extraction of bioactive compounds in Citrus sinesis shells by microwave. The optimization of the extraction parameters of bioactive phytochemicals is important for maintaining the antioxidant properties. Were studied: solvent concentration (51% de acetone v/v), microwave power (500 W), extraction time (122 s), and solid/solvent ratio (25 mL g^{-1}) under the concentration of total phenolics, total antioxidant activity, and individual phenolic acids using the response surface methodology. The authors compared the results with extracts obtained by ultrasound and accelerated solvent extraction. The results obtained with microwave extracts for antioxidant and total phenolic activity were higher than those obtained by other extraction methods.

The extraction of polyphenols from *Olea europppaea* leaves using microwaves and solvent-free was studied by Sahin *et al.,* [79]. Response surface methodology and artificial neural networks were used as tools for predicting and optimizing the number of total phenolics and oleuropein in olive leaf extracts obtained by solvent-free microwave extraction. The antioxidant and antimicrobial activities of the extracts were obtained. Artificial neural networks were the tool that offered the best prediction for the number of total phenolics and oleuropein produced by olive leaves. The optimal extraction conditions were: microwave power of 250 W, extraction time of 2 min, and a sample quantity of 5 g.

Microwave-assisted ultrasonic extraction of polyphenols, flavonoids, triterpenoids, and vitamin C from *Clinacanthus nutans* was developed by Yu *et al.,* [80]. The technology combines ultrasonic cavitation with high microwave energy, in the condition of atmospheric pressure and low temperature, besides providing high yield, time saving and a minimum degradation of the extracts. The optimal conditions of extraction were: solid–liquid ratio 1:55 g mL^{-1}, irradiation power of 90 W, and extraction cycles of 75 s. The results obtained show that the microwave-assisted ultrasonic extraction technology is efficient for extracting bioactive substances from Clinacanthus nutans.

3.3. Supercritical fluid extraction (SFE)

The main characteristic of extraction using supercritical fluid (SFE) is the fact that it presents changes in temperature and pressure, which transform the gas into the supercritical fluid, where the gas and liquid phases are indistinguishable [81].

According to Silva; Martínez [82], SFE is an extraction technique with a mass transfer operation, in which convection in the supercritical solvent phase is generally the main transport mechanism. For Oroian; Escriche [83], in addition to presenting itself as a technique that can be performed on small amounts of samples, the SFE allows for a quick, selective extraction process without requiring additional cleaning.

SFE has desirable transport properties that increase their adaptability. Compared to the liquid solvent, used in conventional extraction processes, supercritical fluids have low viscosity, spreading more easily within the solid matrix, in addition to low surface tension, which allows a quick penetration of the solvent into the solid and, consequently, greater efficiency in the extraction. As the density is related to the solubility, changing the extraction pressure, the force of the fluid can be modified [84]. According to Silva *et al.,* [85], the fluids used in the extraction processes of components in solid matrices under supercritical conditions have desirable properties such as high diffusivity, low viscosity, and low surface tension.

Supercritical fluid extraction is a technology for separating soluble compounds in a fluid under supercritical solvent conditions [86]. Several plant resources are sources of bioactive and nutraceutical compounds that can be extracted from the matrices by supercritical fluid. According to Da Silva *et al.,* [35], the solubility of the extracts depends on the density of the solvent. Thus, different supercritical fluids have been described in studies, such as CO_2; propane; ethane; methanol; nitrous oxide, and water.

Gallego *et al.,* [87], point out that compressed fluids, in the sub and supercritical conditions, are currently used in the extraction of bioactive compounds from natural matrices, contributing to the development of sustainable and efficient technologies. Several applications of

extractions of phenolic compounds, essential oils, pigments, and other bioactive by compressed fluids have been published, in matrices such as plants, algae, microalgae, and food products.

Extraction, isolation, and purification of tetrahydrocannabidiol from *Cannabis sativa* L., where more than 450 chemical components have already been identified, by extraction by supercritical fluid (SFE) in the conditions of temperature between 40 and 80 °C, pressure between 15 and 33 MPa and ethanol as co-solvent between 0 and 5%; and extraction in the solid phase (SPE) (for isolation and purification of extracts) using CO_2 and ethanol as solvents were developed by Gallo-Molina *et al.,* [88]. The effects of temperature, pressure, and ethanol concentration on extraction yields and the tetrahydrocannabidiol content in the extracts were evaluated using central composite planning and response surface methodology.

Kavoura *et al.,* [89], used the SFE technique to extract salvia leaves (Salvia fruticosa). The effects of the studied operating conditions were pressure, temperature, and solvent flow rate (CO_2) under the extraction yield. The extraction yield increased with increasing pressure and the temperature effect depends on the system pressure. The maximum yield was obtained with a pressure of 280 bar and a temperature of 60 °C. The composition of the extracts obtained by SFE was compared with that of extracts obtained by hydrodistillation, confirming the presence of more biologically active compounds in the extracts obtained by SFE.

Morsy [90], produced extracts rich in thymol, which is a key constituent of the flavor of essential oils of ajwain and thyme, fruits of *Carum copticum L.* and aerial part of Thymus vulgaris L. from SFE. The sensory characteristics of the extracts obtained were compared with those of extracts obtained by hydrodistillation and in the extracts obtained by SFE, better results were observed in terms of odor, pungency and aroma. Extraction assisted by supercritical fluid increased the amount of thymol in the extracts of Carum copticum L. and Thymus vulgaris L. compared to hydrodistilled oils, with the best-operating conditions at a temperature of 40 °C and a pressure of 16.7 MPa.

Nagavekar and Singhal [91], optimized the operational conditions (pressure, temperature, and time) of extraction by the supercritical fluid of oleoresin from two species of turmeric. For maximum extraction of oleorenins, curcuminoids, and total volatile compounds, the extraction conditions of Curcuma longa were 350 bar, 65 °C, and 150 min and for obtaining the best antioxidant and anti-inflammatory properties of the beloved Curcuma were 300 bar, 40 °C, and 30 min. Infrared and chromatography analysis revealed the presence of phenolic acids and other important bioactive components in the extracts of *C. amada*. Comparative studies of in vitro bioactivity have shown better results for C. longa.

Pavic *et al.,* [92], used SFE to extract carnosic acid and carnosol from salvia leaves (*Salvia officinalis* L.). The antioxidant and antibacterial capacities of the extracts were evaluated, in addition to the effects of pressure, temperature, and CO_2 flow on the yield of the extract. In the extraction of carnosol, the pressure is a significant variable. As for carnosic acid, the 3 variables studied significantly affect the extraction process. The optimized conditions using the response surface methodology were a pressure of 29.45 MPa, a temperature of 49.19 °C, and a CO_2 flow of 3 kg h^{-1}. The antimicrobial properties of the extracts were tested on 4 types of bacteria and the best results were obtained for Bacillus subtilis. Antioxidant activity of up to 80% has been achieved.

Extraction of polyphenols from leaves of *Callisia fragans*, a plant with medicinal properties, using the supercritical fluid (CO_2) extraction technique was performed by Phan *et al.,* [93]. The antioxidant activity of the obtained extracts was evaluated. The influence of 4 process factors was investigated and the best extraction conditions were: concentration of the ethanol solvent (14%), temperature (45 °C), pressure (200 bar), and CO2 flow (20 g min-1). The study concludes that SFE is a viable alternative for the production of polyphenols with high antioxidant capacity from plant extracts since the efficiency of SFE extraction is higher than that of soxhlet extraction.

Zaid *et al.,* [94], used the supercritical fluid technique in the extraction of lemongrass *Melissa officinalis* L. 1753 (Lamiaceae) and tested the biological activity of the extract in two species of aphids (C. populeti and C. populialbae), in the larva and adult phase. About 20 chemical compounds were identified in the extract of M. officinalis L. and some of them with insecticidal activity in aphids: at the concentration of 0.4 μL mL-1 there was an effect on the larval stages of the two species of Chaitophorus during the first 9 h of exposure. The sensitivity of the two species in the larval phase of aphids to the extracts obtained was greater than in adult individuals. The extract obtained from Melissa officinalis L. can be considered an ecological alternative to synthetic organic insecticides.

Sequential processing of Psidium guajava L. leaf extract, a natural source of antioxidant compounds, by steam distillation and supercritical fluid extraction processes was developed by Silva *et al.,* [85] aiming at obtaining essential oil and non-volatile phenolic components from the process residue. SFE is a widely used technique, offers advantages in the processes of separation of natural products, and in that work was responsible for obtaining the non-volatile components of the extract. The phenolic compounds quercetin and ferulic acid were found and quantified in the strata obtained by SFE. Several authors consider a positive correlation between the presence of phenolic compounds and the antioxidant activity of plant extracts.

Rochefort *et al.,* [95], carried out a study to develop and optimize a methodology for extraction by the supercritical fluid of cannabinoids to fulfill the requirements for obtaining a GMP license to produce pharmaceutical-grade Cannabis. The technique was chosen since it does not require the use of organic solvents to extract the compounds. The variables investigated were: CO_2 flow, time, and pressure through a two-level factorial design. The optimal conditions for extraction were: flow rate of 150 g min^{-1}, 600 min of extraction time, and 320 bar of pressure.

3.4. Pressurized fluid extraction (PLE)

The pressurized fluid extraction (PLE) technique is characterized by a separation process that involves the transfer of solutes from a solid matrix. Liquid solvents are used, employing high temperature and pressure, which produce a reduction in the surface tension of the solvent, which facilitates the penetration of the solvent into the pores of the matrix. The process interrupts the matrix, which increases the mass transfer of the analyte from the solvent sample [96].

According to Mena-García *et al.,* [50], in this green technique, when water is used at its critical point, it can be called subcritical water extraction (SWE) or pressurized hot water extraction (PHWE). Alvarez-Rivera *et al.,* [97], point out the main variables that influence the performance of extraction by supercritical fluid: temperature, pressure, flow rate, and extraction time, in addition to solvent/sample ratio, dispersant, and matrix type. The solvents are chosen based on the solubility characteristics of the desired solute. The versatility of pressurized solvents due to physico-chemical properties including density, diffusivity, and viscosity, which can be controlled by varying the temperature and pressure of the extraction system [98].

According to Santos *et al.,* [98], extraction employing pressurized fluid is an attractive technique, as it allows rapid extraction and reduced solvent consumption, having been successfully applied in the extraction of anthocyanins from various plants. Alvarez-Rivera *et al.,* [97], add that the importance of developing faster, less toxic, and ecological extraction methods have made PLE a popular technique, especially for application in the pharmaceutical and food industries.

Clinacanthus nutans is a medicinal plant of great interest due to the presence of phytochemical components with anti-inflammatory, antimicrobial, and antioxidant activity, and with potential application in the food, chemical and pharmaceutical areas.

Abduljabar *et al.,* [99], studied conventional methods (maceration, infusion, and soxhlet) and modern methods (extraction of pressurized hot water, extraction by supercritical fluid, extraction assisted by ultrasound, and extraction assisted by microwaves) to extract phytochemicals from *C. nutans.* The authors highlight the disadvantages of

conventional extraction techniques such as the high time required the high consumption of solvents and the low efficiency of the extraction process due to the thermal degradation of the phytochemical components. Such disadvantages justify the development of new techniques that offer benefits such as less time and solvent consumption, reduction of toxic waste generation, in addition to ease and low operating costs. The authors point out that PHWE, also known as extraction by pressurized fluid (PLE), operates under conditions of high pressure and temperature that increase the extraction of phytochemicals and uses lower volumes of solvent.

Barbosa *et al.,* [100], used the pressurized fluid extraction technique to separate phenolic compounds with potential antimicrobial and antioxidant activity from *Hancornia speciosa* leaves. The work developed the steps to obtain 3 extracts using the solvents hexane, ethyl acetate, and ethanol. The increase in temperature favored the separation of bioactive compounds. The ethanolic extract obtained at a temperature of 60 °C presented the greatest amount of phenolic compounds and the extract from ethyl acetate at 60 °C presented the greatest amount of flavonoids and rutin.

Çam *et al.,* [101], extracted simultaneously phenolic compounds and essential oil from peppermint leaves (*Mentha piperita* L.) by PLE using water as a solvent and pressure of 10.3 MPa. The simultaneous extraction was carried out in 3 cycles under the best-operating conditions: temperature of 130 °C and time of 10 min. Erythritrine was the main phenolic compound determined in the extract and menthol was the predominant component present in the essential oil.

Jegal *et al.,* [102], evaluated methods for ginsenoside extraction from *Panax ginseng* and *Panax quinquefolius* roots. According to the authors, the total amount of ginsenoside and the extraction efficiency can be increased with the use of advanced techniques in conditions of high temperatures and/or high pressures, such as pressurized fluid extraction, supercritical fluid extraction, and assisted high-pressure extraction by microwave, while traditional ginsenoside extraction techniques are limited by high operating time.

Liang *et al.,* [103], developed and optimized a method for extracting secondary metabolites from *Convallaria majalis L.*, a complex plant matrix, using pressurized liquid extraction. The extraction performance was evaluated by the parameters of analyte stability, recovery (between 63% and 107%), matrix effect on the electrospray interface (ranging from 3 to 27%), and level of co-extracts. The extraction time was 10 min. The work was the first to use the PLE technique to extract secondary metabolites from a complex plant matrix with satisfactory recovery results and a low matrix effect.

Souza *et al.,* [104], evaluated the composition and biological activity of burdock leaf extracts (*Arctium lappa*) obtained by extraction by pressurized fluid and supercritical fluid (CO_2). The two methods were compared based on the parameters extraction yield, chemical composition, phenolic compounds, and antioxidant activity of the extracts. Temperature is considered an important variable since the increase favors the diffusion and solubility of phenolic compounds in different solvents. The extracts obtained by PLE showed higher yield (37.4%) under pressure conditions of 15 MPa and 353.15 K, higher concentrations of chlorogenic acid (1.84%), and rutin (1.46%), in addition to greater antioxidant capacity. Andrade et al studied ultrasound-assisted pressurized liquid extraction of anthocyanins from Aronia melanocarpa pomace, which is the combination of two modern extraction techniques. The anthocyanins were extracted in higher yeld (%) in 45 min to 70 °C, 180 bar, a solvent concentration of 1.5 % wt. citric acid, in a 200 W ultrasound bath. Comparing to classical batch extraction using the same solvent concentration and feedstock, the total anthocyanin content of the extract was increased by 19% [105].

3.5. High-speed homogenization extraction (HSHE)

High-speed shear homogenization extraction (HSHE) method has been used for biocompounds extraction of plant materials based on continuous strong shear and thrust forces. HSHE method presents short extraction times (minutes or seconds) due to the combination of high shear force, severe collision and pressure release. Moreover, it presents high efficiency, mild operating conditions, simple equipment, easy operation, and low costs [106,107].

HSHE has been successfully applied to the pretreatments of fresh hairy root cultures and peels [107].

Guo et al., [107], carried out a study to develop and optimize a methodology for extraction of the anthocyanins from mulberry mediated by NADES. The HSHE was combined with cavitation-burst technique (HSH-CBE). The authors highlight that HSH-CBE technique compared to conventional UAE showed short extraction time and low energy consumption while that anthocyanins extraction yield was higher.

Xu et al., evaluated and optimized high-speed shear homogenization extraction (HSHE) technique for extracting stevioside and rebaudioside A from *Stevia rebaudiana* (Bertoni) leaves. The HSHE extraction procedure was compared with ultrasound-assisted extraction (UAE) and microwave-assisted extraction (MAE) methods. In this study the authors demonstrated the HSHE method has the advantages of low extraction temperature, high efficiency, and low time and energy consumption when compared with traditional techniques [106]. In accordance with these results several reports revealed the potential of HSHE when compared to traditional methods [108,109].

3.6. Electric field pulse assisted extraction (PEF)

Electric field pulse assisted extraction (PEF) is an emerging non-thermal technology that involves high voltage pulses (kV) that are applied in specific short time periods. The most important parameters that affect PEF include electric field strength, pH, treatment time, pulses frequency and shape of the pulse waves [110]. When the electric field is high enough, an electroporation phenomenon occurs increasing cell membrane permeability leading to high extraction yields [111].

The main advantages of PEF are: a) selective extraction of intracellular compounds, b) possibility of developing on-line procedures in automated system c) contributed to minimize deterioration of thermolabile biocompounds through empleated short treatment time and low energy consumption. On the other hand, the main disadvantages are the limitation for lipophilic compounds extraction, the high cost of instrumentation, and the fact that organic solvents cannot be used.

PEF has been used for the extraction of polyphenols from blueberry processing by-products, orange peel, purple-fleshed potato, grape seed, and grape by-products [112]. Pashazadeh et al., [113], evaluated and optimized an extraction method for phenolic compounds from cinnamon using PEF. The authors highlight that the voltage and pulse number of the pulsed electric field influenced significantly in the antioxidant and phenolic activity of the cinnamon extract owing to increased plant cell permeability and contributes to extraction of intracellular components from damaged cells.

Lončarić et al., [112], studied green extraction methods such as high voltage electric discharge (HVED), pulsed electric field (PEF) and ultrasound assisted extraction (UAE) to extract polyphenolic compounds from blueberry pomace. The authors highlight that PEF is a promising green extraction method that can improve the polyphenol extraction performance of blueberry pomace compared to the other methods studied.

3.7. Enzyme-assisted extraction (EAE)

In principle, EAE is based on the enzymatic pretreatment of raw materials to release substances that are bound to the cell walls and thus increase the total yield of extracts and recover target constituents. EAE includes the following main steps: (1) selection and preliminary preparation of raw materials; (2) drying, size reduction, powdering, homogenization; (3) adjustment of temperature and pH; (4) enzyme

addition and incubation; (5) enzyme inactivation; (6) centrifugation and/or filtration; (7) collecting the aqueous phase of the enzymatic extract; (8) other treatments depending on the product requirements (pH adjustment, partial or complete water removal, etc.). Pectinases, cellulases, hemicellulases and ligninases have been the most frequently used enzymes, while, in some specific cases, proteinases may also be used [114].

The combination of enzymes with different extraction techniques [115] has demonstrated to be versatile to recover biocompounds from plant matrices and byproducts. Macedo et al., [115], evaluated the potential of microwave-enzyme-assisted extraction (MEAE) for extraction of phenolic compounds from olive pomace. The authors highlight that the integrated microwave-enzyme extraction achieves higher yields when compared with conventional techniques.

Domínguez-Rodríguez et al., [116], describes the development of an enzyme-assisted extraction (EAE) method to obtain polyphenols retained in the extraction residue from sweet cherry pomace employing three different enzymes. Optimal EAE conditions extracted higher content of proanthocyanidins compared with alkaline and acid hydrolysis. *(Enzyme-assisted extraction of bioactive non-extractable polyphenols from sweet cherry (Prunus avium L.) pomace)*.

Rezende et al., [117], optimized and evaluated an extraction method for bioactive components from monguba (Pachira aquatica Aubl) based on enzyme-assisted extraction (EAE) combined with ultrasonic assisted extraction (UAE). The enzymatic treatments empowered the phenolic extraction, being an alternative to replace solvent-based extraction methods, being safer, since the use of ethanol has been reduced. Even though the cost of the enzymes is relatively high, the application has improved the extraction process, therefore the costs justify its usage, making it a positive investment. These findings show that the enzyme extracts, mainly those obtained from monguba seed, can be used in the development of new functional ingredients.

3.8. Mechanochemical-assisted extraction (MCAE)

Mechanochemical-assisted extraction is an innovative extraction technique, which has been widely used in the extraction of bioactive compounds from plant materials. Mechanochemistry is a branch of the chemistry, which is refers to the chemical or physicochemical transformations generated by mechanical force [118].

According Wu et al., [119], three steps define the MCAE: mechanical pretreatment of the raw sample, mechanochemical treatment of the pre-activated materials with solid reagent and grind under high-intensitive mechanical, and subsequent extraction procedures. The extraction of bioactive compounds through mechanochemistry is a procedure that is in accordance with the principles of green and sustainable chemistry, as it makes it possible to avoid or considerably reduce the use of organic solvents, which, depending on their nature, can be toxic [120].

MCAE can destroy vegetal tissues during grinding, and the addition of alkali can react with the components in the plant to increase the solubility of the original substances, which increases the yield of extracted substances [121]. In the mechanical activation, impact-shearing on the particles of the material is accompanied by destruction of the cell wall that facilitates the isolation of the substances in the processed material. The extraction time is reduced because of mechanicochemical treatment increase the effective surface area of the components [122]. Mechanochemical processing resulted in particle size reduction and intimate contact between the milled materials.

MAE has gained a lot of attention in the food and pharmaceutical industry because of its superiorities: high efficiency, low operating temperature and no or less consumption of organic solvent, since water can be used as an extraction solvent [119]. The effectiveness of MCAE procedure depend on important factors: type and concentration of the solid reagent, milling time, extractions time and temperature, liquid/solid ratio and acidification pH value.

Mechanochemical-assisted extraction study of triterpenoids from *Antrodia Camphorata* was performed by [121]. Compared with the ethanol hot thermal reflux method, MCAE afforded an increased yield of triterpenoids to 1.82 ± 0.04% under conditions of mixing with 10 wt% $NaHCO_3$, milling for 20 min, and extracting with water and chloroform.

Mechanochemical-assisted extraction of hesperidin *from Pericarpium Citri Reticulatae* was researched in AGO-2 high intensity planetary activator [122]. Supporting to optimize extraction efficiency, several variables were varied and the optimum MCAE conditions were obtained: Na_2CO_3 content of 30.0% (w/w), grinding time 20 min, extraction temperature 20 °C, extraction time 10 min, liquid/solid ratio of 80:1 mL g^{-1}.

Rincón et al., [123], evaluated the mechanochemical extraction of antioxidant phenolic compounds from bay leaves (*Laurus nobilis)*. The results were compared with other extraction techniques: conventional Soxhlet, ultrasound and microwave and MCAE exhibited satisfactory results. The use of Li_2CO_3 as solid reagent provided comparable total phenolic content to conventional extraction with reduced extraction time.

Wang et al., [124], used the mechanochemical extraction for develop the method of extraction of bioactive substances (alkaloids, flavonoids, and catechins) from plants using deep eutectic solvents. The research demonstrates an extraction method for obtaining bioactive compounds from tea leaves presenting as advantages fast, highly efficient, and ecofriendly strategy.

Mechanochemical-assisted extraction method was developed and optimized for extraction of flavonoids and terpene trilactones from Ginkgo biloba leaves [125]. The MCAE parameters was studied and the processing conditions were: amount of solid reagent ($NaHCO_3$) 21%, milling time 7.5 min, and ratio of solvent to solid 33 mL g^{-1}. Compared the method of MCAE with the heat reflux extraction, the yields of flavonoids and terpene trilactones are higher, and the extraction time was shortened and only used water as solvent.

Xie et al., [126], used the mechanochemical-assisted extraction for the extraction of rutin from leaves of *Hibiscus mutabilis* L.. The process was carried out via mechanochemical pretreatment in AGO-2 high intensity planetary mill and the yield of rutin was obtained by grinding *H. mutabilis* with Na_2CO_3 (15.0 wt%) and $Na_2B_4O_7{\cdot}10H_2O$ (1.5 wt%) for 4 min, extraction temperature at 25 °C, total extraction time of 15 min, acidification pH 5.0 and solvent/material ratio of 25 mL g^{-1}. Compared this results with heat reflux and superfine grinding extraction, MCAE showed the advantages of efficiency, no organic solvent consumption and lower extraction temperature.

Xie et al., [127], studied a mechanochemical-assisted extraction of flavonoids from bamboo (*Phyllostachys edulis*) leaves. The highest recovery of flavonoids was achieved by grinding the leaves with Na_2CO_3 (12 wt%) and $Na_2B_4O_7{\cdot}10H_2O$ (2.0 wt%) for 10 min, extraction with water at 25 °C and liquid/solid ratio of 20 mL g^{-1} for time of 15 min. The method was compared with heat reflux extraction and alkali extraction and both of which yielded lower recoveries of total flavonoids and representative flavonoids. The work showed the advantages of efficiency, no organic solvent consumption and much lower extraction temperature in the use of the MCAE.

Mechanochemical extraction tool was used for extraction of magnolol with low-pollution from stalk barkof *Magnolia officinalis* [128]. The process was carried out using a high intensive activator, AGO-2. The yield of magnolol was maximized in the conditions: milling with Na_2CO_3 (2.0 wt%) for 7 min; extraction by water at 40 °C and liquid/solid ratio of 25:1 mL g^{-1} for 20 min; precipitation at pH 3.5. The technique was compared with superfine grinding extraction and heat-reflux extraction, and the MCAE reduced the extraction time and temperature, besides no requirement of organic solvent consumption owing to the transformation of magnolol into a water-soluble salt form.

4. Green solvents

In a typical process, solvents are widely used to dissolve reagents,

affecting chemical reactivity, extracting and washing products, and to separate mixtures. Conventional organic solvents are not only ecologically dangerous but also direct acute and chronic toxicity, in addition to presenting carcinogenic potential. To improve the protection of health and the environment against the risks associated with the use of hazardous organic volatile solvents, great efforts have been and are being devoted to the development of alternative means of green reaction [129].

Precautions to minimize the effects of these solvents by improved recycling processes are of limited success and cannot prevent some losses to the environment. Also, the risk associated with possible accidents is still present. For these reasons, the substitution of these hazardous solvents by alternative green sustainable solvents seems to be the only valid alternative for sustainable use of solvents [130]. For this reason, the search for meeting the principles of green chemistry has grown, such as the use of green solvents in relation to toxic solvents, with an increase in works involving green chemistry and the use of green solvents of approximately 66 and 68% compared the last ten years (Fig. 5), respectively.

Greener procedures need a balance between the analytical performance and Green Analytical Chemistry principles and requirements, mainly in extraction to determine of bioactive compounds in natural products [58] (Fig. 6). The development of sustainable and efficient analytical methodologies involves the application of innovative tools, such as miniaturization, automation, use of portable low-cost instruments, simplification of sample prep procedures, and the use of Artificial Intelligence for analytical purposes. The analytical GREEness approach and software recently proposed by Pena-Pereira is an excellent and complete tool to objectively estimate the sustainability of analytical methodologies because it is based on the twelve principles of Green Analytical Chemistry (GAC) [131]. Undoubtedly, solvents are by far the factor with the most incidence in the battle for "greening" experimental schemes and the design of green solvent for the replacement of harsh organic solvents is an urgent need.

In this context, the best alternative is the development of "solvent-free" procedures though in the majority of cases the use of solvents is unavoidable. Over the past twenty years, Ionic liquids (ILs), presented by Paul Walden in 1914 [132], have gained significant importance. Ionic liquids are organic salts consisting entirely of ions with melting points lower than 100 °C. However, IL "greenness" is often challenged; in general, they are expensive, and some of them are toxic, unstable, and flammable.

Recently, Natural Deep Eutectic Solvents (NADES), prepared from bio-based starting materials (with hydrogen bond donors and acceptors to form a eutectic mixture) have emerged as contestants for green extraction. However, it is still possible to observe in Fig. 7 that the use of Deep Eutectic Solvents in research remained superior in recent years to the Natural Deep Eutectic Solvents, with this increase of 46.22% in the year 2020. Directing an indicative view towards knowledge which covers the use of the term and the application aspects that involve it, mainly in research involving the questions addressed within the theme of green chemistry.

Ionic liquids and natural deep eutectic solvents are greener options compared to conventional solvents in terms of biocompatibility. Both of them show a wide liquid range, low volatility, and can dissolve organic and inorganic compounds in a wide range of polarity [133]. Whereas ILs and DESs have some common features, especially physical properties and applications, they are two completely different families of substances comparing their chemical nature.

In comparison to ILs, NADESs offer several advantages; including cost, ease of preparation, stability, and 'tunability" [134]. A drawback for NADES is related to their short life; so further research is indeed to better understand their structure and mechanism of formation to develop tools for their design to specific extraction needs.

4.1. Natural eutectic solvents

Because of all existing restrictions and the growing need for the use of new solvents, so-called deep eutectic solvents (DES) appear. These new solvents have been widely recognized as being a kind of ecological substitute for conventional solvents [135].

According to Dai *et al.,* [136], newly formed liquids have significantly lower melting points than any of the individual components. When DES's are composed of primary metabolites such as amino acids, organic acids, and sugars, they are also called deep eutectic solvents (NADES).

DES's have a variety of useful properties, with low volatility, adjustable viscosity, and miscibility in water. Consequently, they are considered effective solvents for the dissolution and extraction of a wide range of polar and nonpolar compounds. In addition to having a lower environmental and economic impact, they have other advantages as solvents, such as biodegradability, low cost, simple methods for preparation, and the fact that the precursors used are renewable, non-toxic, and natural compounds [137].

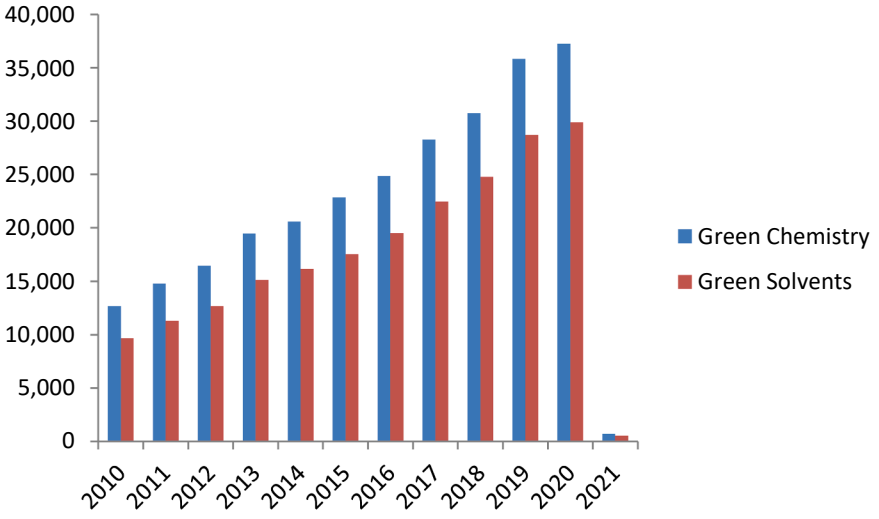

Fig. 5. Publications using the keywords: Green chemistry; Green Solvents, among 2010 and August 25, 2021(Science Direct). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

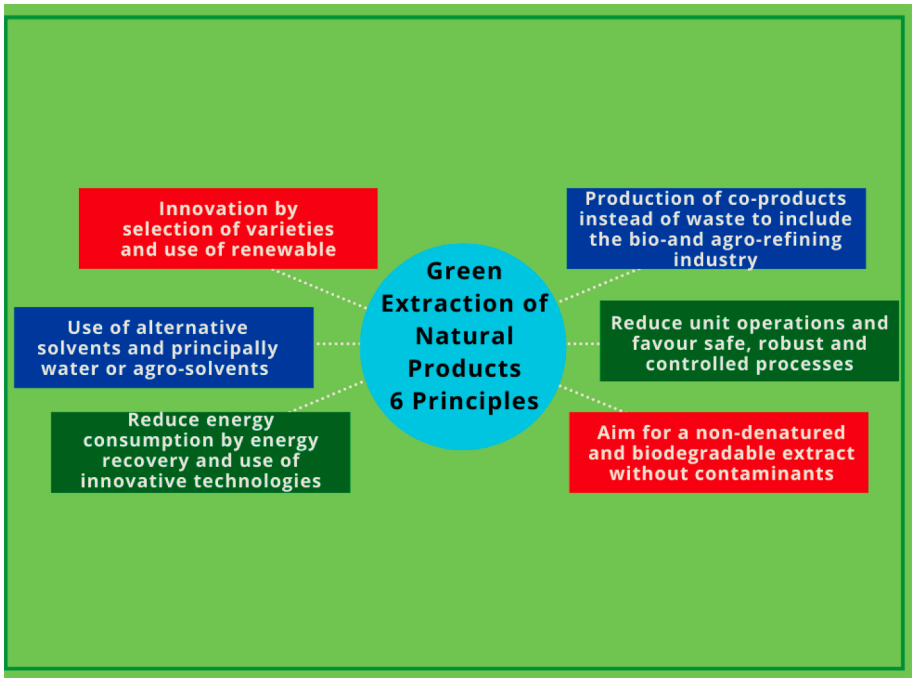

Fig. 6. The Principles of Green Extraction of Natural Products. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

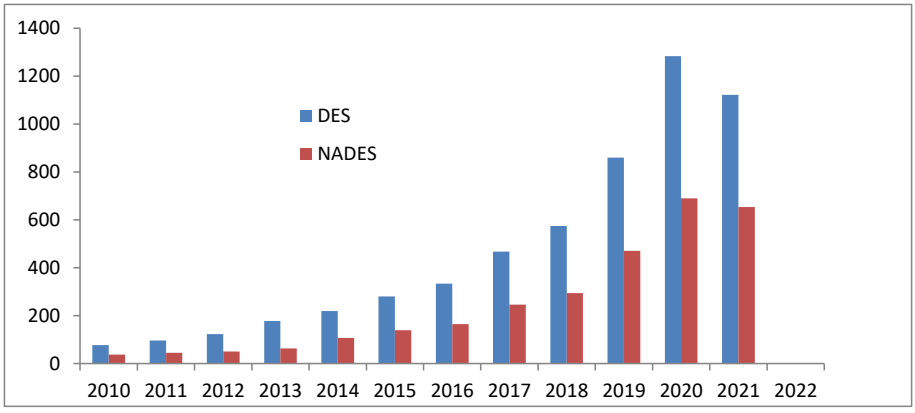

Fig. 7. Publications using the keywords: deep eutectic solventes (DES); natural deep eutectic solventes (NADES), among the years 2010 to May 17, 2021 (Science Direct).

Eutectic solvents are generating increasing interest within the scientific community, which is still in the process of a real understanding of the specific characteristics of these fluids. In recent years, these types of solvents have been used in the most diverse forms of application, such as chemical catalysis, organic synthesis, electrodeposition, and enzymatic reactions [136].

Despite the growing interest in the different separation processes, there is still a lack of information on practical aspects related to their application as extraction solvents, that is, their efficiency and ideal physical properties, such as viscosity and polarity. However, few studies still point to a focused focus on the application of DES's in the extraction of bioactive compounds from plant materials, for example [138].

Currently, great attention is paid to deep eutectic solvents (NADES) for the microextraction process. This reality becomes possible in the face of a scenario of uninterrupted search for the development of a continuous flow method with new extraction systems focused on rapid extraction and separation kinetics, which does not generate environmental impacts, with high affinity for the target analytes, in addition to compatibility with flow and detection systems [139].

According to Shishov *et al.,* [140], there are a variety of automated procedures that use NADES as solvents for extraction procedures, and which are still widely indicated in the literature.

It has recently been demonstrated that NADES has unique properties for the liquid–liquid microextraction process, such as dispersing solvents. In the aqueous phase, NADES can be soluble in the extraction solvent, however, unlike conventional dispersing solvents (polar organic solvents), NADES is based on quaternary ammonium can be decomposed in the aqueous phase [141,142].

DES's are characterized by having high viscosity and they can exist in a solid-state at room temperature, which is why they can be used successfully in the process of extracting active compounds from natural products. As an example, it is the use of DES's as a means of extracting glycerin from blends of aromatic naphtha biodiesel [143].

In a study with the extraction of phenolic compounds from virgin

olive oil using deep eutectic solvents, García *et al.,* [137] observed that the results suggest that DES offers an efficient, safe, sustainable solution, in addition to being an economical alternative to methanol for the extraction of bioactive compounds in virgin olive oil (VOO). In the research, different combinations of DES made up of Choline Chloride (ChCl) were used in various mixing proportions with sugars, alcohols, and organic acids.

The method with application in different combinations of deep eutectic solvents, also provides some important advantages, such as the simplicity of experimental steps, mainly the use of low toxicity solvents, since most DES's can be prepared from chemicals easily. accessible, especially DES's derived from ChCl and renewable chemicals, with relatively high speed in sample preparation [47].

Natural Deep Eutectic Solvents (NADES) were coined in 2011 as revolutionary green media. These eutectic mixtures are formed by cellular constituents such as sugars, alcohols, amino acids, organic acids, and choline derivatives. The nature of the interactions that take place is hydrogen bond and Van der Waals forces. In the NADES matrix, the hydrogen-bonding network via intermolecular interactions modifies their physicochemical environment. Interestingly, they have been proposed as the third solvent in living cells, explaining their high solubilizing and stability capacity of natural compounds [144]. NADES stands out for being design solvents with tunable physicochemical properties due to a large number of potential combinations (around 106). Also, they present competitive costs, greenness, and simple preparation [136,145]. Methods most commonly used for preparing NADES are heating and stirring [136,146,147] evaporating method [136], and freeze-drying method [148]. Recently, a greener microwave-assisted approach for the preparation of NADES in the shortest time was proposed by Gomez et al., [149].

Since NADES (Fig. 8) have emerged, most of the applications have been focused on bioactive compounds extraction from natural sources [150]. When analyzing the publications concerning NADES applications in medicinal plants (Fig. 7) a notable increase is observed demonstrating the growing interest in this area.

Analytical characteristics of representative articles concerning the extraction of compounds from medicinal plants mediated by NADES are provided in Table 2. As can be seen, the eutectic mixtures composed of organic acids, sugars, and choline chloride are the most commonly used as extraction media. The high viscosity of the NADES restricts the mobility of the analytes inside the NADES during the extraction. In this sense, water is currently added as an integral NADES constituent or after their preparation as a diluent to improve the mass transfer process [151,152].

The biologically active compounds evaluated include flavonoids, phenolic acid, anthocyanin, terpenoids, and alkaloids, which indicate the possible utilization of NADESs in the extraction of various polar, as well as non-polar, natural compounds [150]. Among the phenolic compounds are by far the most studied (Table 2).

Conventional extraction techniques such as Soxhlet, maceration, decoction, infusion, present some drawbacks such as long extraction periods, high solvent, and energy consumption that makes them harmful from an environmental perspective [153]. Non-conventional techniques, including microwave-assisted (MW) and ultrasound-assisted extraction (UAE), have gained great interest since they reduce the use of toxic organic solvents, improving sample throughput and efficiency [154]. As can be seen in Table 2 UAE is the approach most applied.

Several reports compared NADES extraction efficiency with traditional solvents such as organics and water. The results demonstrated outstanding extraction capacity of NADES for both polar and weak polar compounds [155-157].

Medicinal plants constitute a rich source of bioactive compounds with different biological activities such as cardio-protective, anti-inflammatory, and antimicrobial [150]. Based on the aforementioned, the green extraction of plant bioactive compounds mediated by NADES opens interesting possibilities for the development of new drugs, functional foods, and food additives. It is important to highlight that eutectic mixtures are formed by food-grade ingredients which could be directly applied without purification steps.

Considering that control in green chemistry allows the possibility to compare different methods and critically select the greenest option; recent trends encourage analytical chemists to apply sustainable metrics to achieve the greenness of an extraction technique [149].

With the aim of the mainstream green concept, it is of utmost importance to move from general principles to practice. In this sense, NADES are undoubtedly the solvents of future industry and efforts should be made to evaluate them on an industrial scale [134].

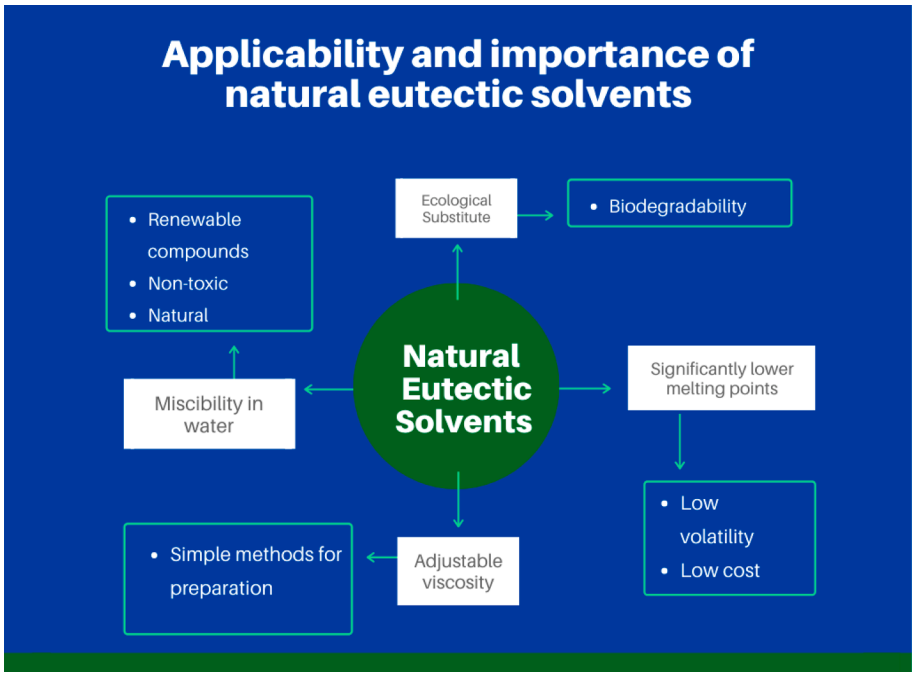

Fig. 8. characteristics of natural deep eutectic solvents.

Table 2
Application of NADES for extraction of phenolic compounds in medicinal plants.

NADES	Medicinal Plants	Biocompounds	Extraction technique	Reference
Lactic acid:dextrose: water (5:1:10)	Larrea divaricata Larrea cuneifolia Thymus vulgaris Origanum vulgare	Total phenolic content	UAE -ratio plant/solvent: 75 mg mL–1 -time: 42 min -temp: 40 °C	[154]
Choline Chloride: glycerol (2:1 w/w)	Cinnamomum burmannii Caesalpinia sappan	Brazilin	UAE -ratio plant/solvent: 1:2 w/w -time: 50 min -temp: ni -water added: 47.57%	[177]
		Phenolic compounds: Trans-cinnamaldehyde and coumarin	UAE -ratio plant/solvent: 1:8 w/w -time: 30 min -temp: *ni* -water added: 20%	
Lactic acid:fructose: water (5:1:11)	*Rhodiola rosea*	Salidroside, tyrosol, rosavin, rosin, and cinnamyl alcohol, phenylethane and total phenylpropanoids	UAE -time: 154 min, -temp: 22 ∘C -ratio plant/solvent: 50 mg mL^{-1}	[155]
Sucrose:citric acid : water (1:1:10) Proline:malic acid: water (1:1:3) Fructose:sucrose: glucose:water (1:1:1:11) Glucose:choline chloride:water (2:5:5)	*Myrothamnus flabellifolia*	Anthocyanins and phenolic compounds (metabolomic analysis)	Heated: 50–55 °C UAE: -time: 90 min -ratio plant/solvent: 50 mg mL^{-1} -water added: 25 %	[151]
β-alanine–citric acid (1:1); 50% water Proline–citric acid (1:1); 40% water	*Scutellaria baicalensis*	Flavonoids (baicalein, scutellarein, wogonin, oroxylin A and their glycosides, baicalin, wogonoside and oroxyloside)	Water bath: 40 °C, 60 min. UAE: -time: 30 min -temp: room temperature -ratio plant/solvent: 50 mg mL^{-1} Clean-up: solid phase extraction (SPE).	[156]
Choline chloride: fructose: water (2:1:1)	*Aronia melanocarpa*	Phenolic compounds (21), total phenolic, flavonoids and anthocyanin content	UAE -ratio plant/solvent: 200 mg mL^{-1} -time: 20 min -temp: 35 ∘C	[178]
Glycerol: nicotinamide (5:1)	*Moringa oleifera L.*	Phenolic compounds (8) and total phenolic content	-ratio plant/solvent: 28.5 mg mL^{-1} Pretreatment: 23 °C, 30 min. Thermostated hot plate: -temp: 50 °C, -time: 150 min -stirring: 500 rpm.	[157]
Lactic acid, dextrose (5:1); 15% water	*Larrea cuneifolia*	Total phenolic content	UAE -ratio plant/solvent: 75 mg mL^{-1} -time: 42 min -temp: 40 °C (±2°C)	[179]
Lactic acid:dextrose: water; (5:1:10)	*Larrea cuneifolia Larrea divaricata*	Phenolic compounds (caffeic, ferulic rosmarinic, and nordihydroguaiaretic acids,quercetin, apigenin ,tyrosol) and alkaloids (:theophylline, piperine,harmaline,theobromine, caffeine)	UAE -ratio plant/solvent: 75 mg mL^{-1} -time: 42 min -temp: 40 °C (±2°C)	[152]
Glycolic acid:Betaine	*Galium species (G. verum, G. album, G. rivale, G. pseudoaristatum,* and *G. purpureum)*	Phenolic compounds	DLLME -sample: 10 mg, -solvent medium (water; NaCl: 10%; NADES: 15% or β-cyclodextrin: 1%): 700 μL -extraction solvent (ethyl acetate): 400 μL -dispersive solvent (ethanol): 300 μL -vortex time: 30 s, -extraction time: 1 min	[180]
	Ruta graveolens L.	Total phenolics content		

(*continued on next page*)

Table 2 (*continued*)

NADES	Medicinal Plants	Biocompounds	Extraction technique	Reference
Choline Chloride: citric acid (2:1); 20% water			Stirring -ratio plant/solvent: 13.3 μg mL^{-1} -time: 90 min	[92]
choline chloride : levulinic acid (1:2); 50 % water	*Jinqi Jiangtang* formula, composed by *(Coptis chinensis, Astragalus membranaceus, and Lonicera japonica)*	Chlorogenic, neochlorogenic and isochlorogenic acid, coptisine,groenlandicin and berberine	UAE -time: 60 min -ratio plant/solvent: 8 mg mL^{-1} -temp: *ni*	[181]
Choline chloride: fructose (5:2)	*Crinum powellii and Crinum bulbispermum*	Alkaloids	UAE -ratio plant/solvent: 0.4 g mL^{-1} -time: 60 min -temp: 40 °C -centrifuged: 4000 rpm, 20 min	[182]
choline chloride: fructose (5:2); 35 % water (v/v)	*Crinum powellii*	Alkaloids (lycorine crinine,crinamine)	UAE -time: 60 min -temp: 50 °C -ratio plant/solvent: 400 mg mL^{-1}	[183]
Lactic acid: dextrose (5:1); 15% water (v/v)	*Larrea cuneifolia*	Phenolic compounds (tirosin, catequin, cinnamic acid, naringenin, nordihydroguaiaretic acids, caffeic acid, ferulic, rosmarinic, Api, rutin, quercetin and luteolin)	UAE optimal conditions: -ratio plant/solvent: 75 mg mL^{-1} -time: 42 min -temp: 40 °C (±2°C) -centrifuged: 10000 rpm, 30 min	[152]
Choline chloride: citric acid (1:1); 40% water	*Moringa oleifera*	Phenolics compounds (hydroxycinnamic acid, flavonoids) and glucosinolates	UAE -ratio plant/solvent: 100 mg mL^{-1} -time: 60 min -temp: 50 °C	[154]
Lactic acid: glucose, (5 : 1); 10 % water	*Rheum palmatum* L.	Anthraquinones: chrysophanol, rhein, emodin, aloe-emodin and physcion	UAE -time: 1.5 h, -temp: 82 °C -ratio plant/solvent: 38.46 mg mL^{-1}	[184]
Choline chloride: maltose (1:2); 20% water	*Cajanus cajan*	Phenolics compounds (orientin; vitexin;luteolin; apigenin; isorhamnetin;formononetin;pinostrobin chalcone; pinostrobin;longistyline; cajanin- stilbene acid;cajanus-lactone; cajanol; apigenin-6,8-Di-C-α-L-arabinoside;apigenin-8-C-α-L-arabinoside)	MAE -ratio plant/solvent: 33,33 mg mL^{-1} -time: 12 min -temp: 60 °C	[138]

UAE: ultrasound assisted extraction.
MAE: microwave assisted extraction.

4.2. Ionic liquids

Ionic liquids (IL's) are organic salts made up of organic cations and organic or inorganic anions such as chloride, dicyanamide, trifluoroacetate, with melting points below 100 °C. They are considered green solvents, taking into account their exclusive properties, such as negligible vapor pressure over a wide temperature range, high thermal stability, and high viscosity. In addition to presenting improved profits and operations, described for various industrial processes, these solvents can also be recovered and final products with only traces of residual solvent can be obtained [158].

The unique properties of IL's, such as high solubility, high thermal, chemical, and electrochemical stability, and non-flammability, make them suitable for use in different areas, such as process technology, organic synthesis, electrochemistry, and analytical chemistry. In the field of biotechnology, IL's can be applied as substitutes for hazardous volatile organic solvents in catalytic processes, as well as in the extraction and separation processes of biologically active compounds [159].

According to Abu-Eishah [160], among the available technologies, IL's regeneration can be performed by conventional operations, such as distillation and extraction. Volatile products can be easily isolated from IL's by distillation in mild conditions, while low volatility products can be separated by extraction or membrane processes, such as nanofiltration and evaporation.

Even though IL's are defined as environmentally friendly solvents due to the mentioned properties, it is important to pay attention, as they can still reach soils, surface, and underground water through accidental spills or effluents [161].

According to Kudłak *et al.,* [162], accumulations often occur in the environment and in higher organisms that adversely affect homeostasis. Consequently, the sorption, biodegradability, and toxicity of IL's, as well as their degradation products, are of high importance for their impact and final destination in the environment.

In an investigation on the application of alcohols, esters, and ionic liquids (IL's) as alternatives to conventional organic solvents in the liquid–liquid extraction of Quercetin from different medicinal plants, flowers, and frozen red onion (Allium cepa L.), Domańska et al., [163], evaluated the parameters that affect the extraction yield using IL's, such as chemical structures of the IL cation and anion, the volume ratio of the extraction solvent phase, the extraction time and the sample form and Quercetin concentration. The most efficient extraction of the aqueous phase was obtained using water-soluble IL's.

The hydrophobic interaction between water-insoluble IL's and Quercetin is predominant due to their lower hydrophobicity and increases proportionally to the length of the alkyl chain of the IL cation, increasing the extraction capacity of some IL's [163].

The class of IL's that present the imidazolium cation is intended for the development of various processes and materials due to easily adjustable properties through structural changes in the cation and anion, as well as capacity in their self-organization [164].

5. Green analytical chemistry metrics

The ultrasound-assisted, microwave-assisted, supercritical fluid, pressurized fluid techniques for the extraction of the bioactive compounds in aromatic and medicinal plants in association with environmentally friendly solvents (Fig. 9), reported in this review have as main advantages, the reduction of extraction time, solvent consumption, extraction yields, and reproducibility, as mentioned by Oreopoulou *et al.,* [165] works reported in the literature have proposed criteria and parameters to measure the degree of analytical procedure sustainability.

Some authors have developed parameters to assess whether chemical procedures fall under the concept of green or sustainable analytical chemistry, among the factors evaluated to quantify and be able to assess whether analytical methods are following green chemistry, for example, type and volume of reagents, waste generation, the number of procedural steps, miniaturization and automation and energy consumption [131].

Some authors use as a way of trying to measure the environmental impacts of the developed extraction methods some parameters associated with energy efficiency: electrical consumption (Ec) in KWh and relative electrical consumption (E*c) in KWh g^{-1}, whose calculations can be seen respectively by equations (1) and (2) [166].

$$Ec = \frac{Pt}{1000} \tag{1}$$

Where, P is power consumption (W) and t is time (s)

$$E^{*}c = \frac{Ec}{x} \tag{2}$$

Where m is mass or volume of extract.

In addition to energy consumption, another important parameter is (Eco_2) emission in g and the relative CO_2 emission [166], (equation (3) and (4)).

$$Eco_2 = \frac{Ec800}{1000} \tag{3}$$

The relative CO_2 emission for diferents extraction techniques can be calculated using the equation (4)

$$E^{*}co_2 = \frac{Eco2}{x} \tag{4}$$

In Table 3, it is possible $_2$ to observe that the methods assisted by ultrasound and enzyme-assisted extraction are low cost, from a techno-economic point of view, in addition to being considered more ecologically correct when considering the factors of energy consumption and CO_2 emission. especially when compared to microwave, supercritical fluid and pressurized fluid extractions. However, there are other important parameters that will influence the determination of whether or not an analytical procedure is environmentally friendly "green". However, it is necessary to evaluate other factors that are part of the 12 principles of green analytical chemistry.

In order to facilitate whether an analytical method or procedure follows the principles of green analytical chemistry, Pena-Pereira *et al.,* developed a tool for evaluating analytical procedures from the point of view of green analytical chemistry, the software AGREE (Fig. 10) [131]. Based on this tool, some works reported in the literature on the extraction of bioactive compounds were evaluated according to the criteria developed by these authors. Table 4 presents the results of the evaluation using the index obtained based on the 12 requirements required by the tool using the software AGREE it was possible to see that the assisted extraction procedures can be considered medium green, as it is necessary to take into account the toxicity and volumes of solvents used in the extraction. So, substitution by non-toxic solvents would make these procedures highly green, that is, according to the principles of sustainable chemistry.

6. Conclusion

There is a growing harmonious need for processes involving research with a vision based on the aspects that lead to the sense of sustainability, which ends up becoming one of the greatest challenges for science in the present century. In the area of analytical chemistry, countless problems compromise a good development of the analyzes, and even potential reuse of the established techniques, including the misuse of reagents, for example. This, in its broad sense, ends up generating accelerated impacts, often causing even eminent risks for those working in the handling process, leading to inappropriate discards and unprecedented consequences, over the long term.

Therefore, considerations regarding aspects related to the dissemination of metrics that evaluate and condition green analytical procedures to become highly relevant, where in addition to taking into account environmental aspects, it becomes essential, and these can be considered essential indicators or even optional, in the presentation of definitions, compilations, relevance, and even reference base.

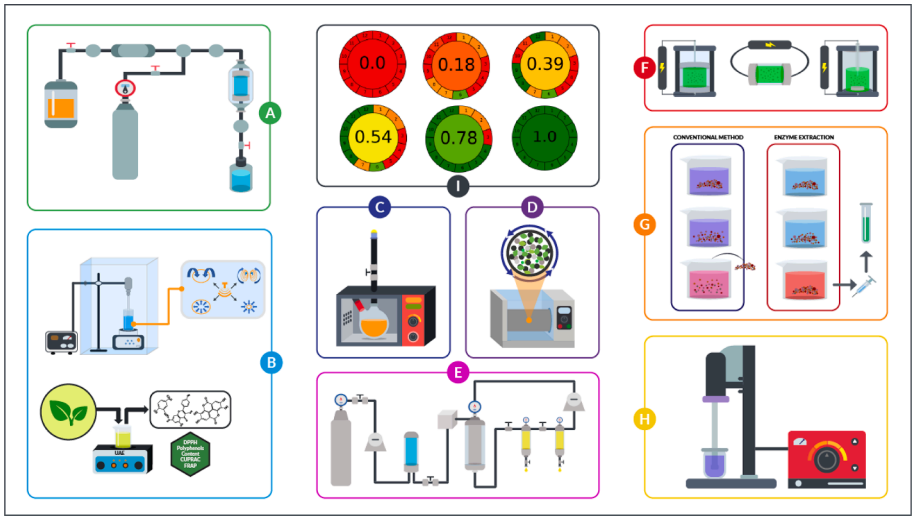

Fig. 9. Assisted Extraction Techniques. Legenda: A – Pressurized Fluid Extraction (PLE); B – Ultrasound-Assisted Extraction (UAE); C – Microwave-Assisted Extraction; D – Mechanochemical-Assisted Extraction (MCAE);E – Supercritical Fluid Extraction (SFE);F – Electric field pulse assisted extraction (PEF);G – Enzyme-Assisted Extraction (EAE);H – High-speed homogenization extraction (HSHE);I – AGREEmetric.

Table 3
Energy efficiency, CO_2 emission, Cost (kEuros) for extraction techniques green chemistry evaluation.

Sample	Analyte	Extraction technique	Electric Consumption (KW h)[a]	Relative Electric Consumption (KW h L^{-1})[a]	CO_2 emission (g)[a]	CO_2 emission relative[a]	Cost[b]	Ref.
Physalis[1]	Catechin, rutin, caffeic acid and *trans*-cinnamic acid	ultrasound	0.014	0.96	0.0115	0.77	low	[29]
Croton[2]	Gallic, vanillic, syringic, *p*-coumaric, caffeic, ferulic, quercetin and kaempferol	ultrasound	0.003	0.18	0.0022	0.15	low	[58]
Quercus[3]	Catechin, epicatechin, epigallocatechin, syringic, *p*-coumaric, synaptic and naringenin	microwave	0.045	5.6	0.04	4.5	medium	[72]
Psidium and *Smilax*[4]	Gallic and ellagic acids, quercetin and *trans*-resveratrol	microwave	0.18	6.0	0.15	4.8	medium	[161]
Salvia[5]	8 bioactive compounds	supercritical fluid	0.125	10.4	0.10	8.3	high	[87]
Mentha[6]	5 bioactive compounds	pressurized fluid	0.06	3.7	0.045	3.0	high	[99]
Arctium[7]	Gallic acid, dihydroxybenzoic acid, chlorogenic acid and rutin	pressurized fluid	0.06	3.1	0.045	2.5	high	[102]
Hovenia[8]	Polyphenolic-Protein-Polysaccharide Complexes	enzyme-assisted extraction	0.09	0.9	0.072	0.72	low	[185]

Physalis angulata L.[1]; Croton heliotropiifolius[2]; Quercus (Q. robur L.)[3]; Psidium guajava Linn and Smilax china[4]; Salvia fruticosa[5]; Mentha piperita L.[6]; Arctium lappa[7]; Hovenia dulcis[8]. KUSUMA et al., (2019)[a] [166]; CHEMAT et al., (2020)[b] [167].

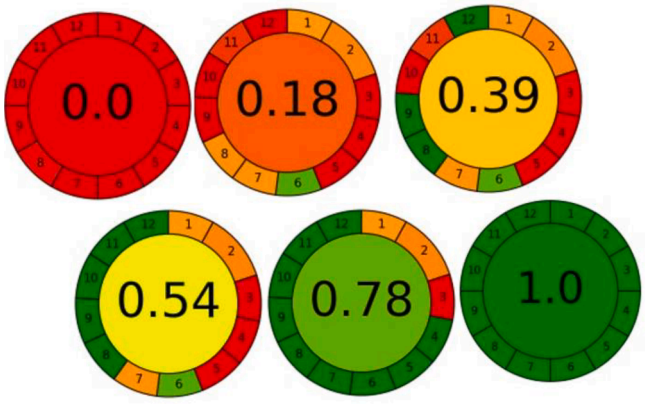

Fig. 10. Green analytical chemistry metrics (AGREE) [117]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In this regard, among various principles that govern change on the way to sustainability, the adjustment of the laboratory and industrial systems are the ones that must be observed, widely discussed, and used, considering the importance of developing analytical methods and procedures aligned with the principles of chemistry green analytics.

7. Novelty statement

The growing awareness of environmental issues and the growing need to reduce the use of toxic products not only in chemistry, but also medicine and even in industry, in view of their effects and the consequent risk to human health, has presented chemistry green as an area of great interest among researchers of analytical chemistry of natural products.

Green analytical chemistry aims to design environmentally benign chemical processes and synthetic methodologies to eliminate or reduce the use of dangerous and toxic chemicals at any stage of production in industry or even in the laboratory. As the development of ecological methods is cheaper than cleaning the polluted environment, ecological analytical methodologies must be made very attractive from an aesthetic and economic point of view.

Table 4
Green analytical chemistry metrics for procedure extraction evaluation.

Medicinal plant Sample	Analyte	Extraction technique	Ration mass/solvent	Analytical technique	metrics	Reference
Physalis angulata L.	Catechin, rutin, caffeic acid and *trans*-cinnamic acid	ultrasound	0.6 g 15 mL^{-1}	HPLC	0.58	[29]
Croton heliotropiifolius	Gallic, vanillic, syringic, *p*-coumaric, caffeic, ferulic, quercetin and kaempferol	ultrasound	0.2 g 11.4 mL^{-1}	HPLC	0.63	[58]
Quercus (*Q. robur* L.)	Catechin, epicatechin, epigallocatechin, syringic, *p*-coumaric, synaptic and naringenin	microwave	5 g	HPLC-MS	0.53	[72]
Psidium guajava Linn and *Smilax china*)	Gallic and ellagic acids, quercetin and *trans*-resveratrol	microwave	1 g 20 mL^{-1}	HPLC	0.61	[161]
Carum copticum L. and *Thymus vulgaris* L.	21 bioactive compounds	supercritical fluid	5 g of sample and CO_2 flow (8 mL min^{-1})	CG-MS	0.58	[88]
salvia fruticosa	8 bioactive compounds	supercritical fluid	40 g of sample and CO_2 flow between 1 and 3 kg h^{-1}	CG-MS	0.55	[87]
Mentha piperita L.	5 bioactive compounds	pressurized fluid	10 g of sample	HPLC	0.60	[99]
Arctium lappa	Gallic acid, dihydroxybenzoic acid, chlorogenic acid and rutin	pressurized fluid	7.5 g of sample and 2 mL min^{-1} of solvente flow	HPLC	0.58	[102]

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.

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Further reading

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