New phases for analytical scale extraction from plants: Current and future trends

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New phases for micro-scale extractions from plants: current and future trends

Giulia Mastellone[§], Arianna Marengo[§], Barbara Sgorbini, Patrizia Rubiolo, Cecilia Cagliero*

[1]*Dipartimento di Scienza e Tecnologia del Farmaco, Università degli Studi di Torino, I-10125, Turin, Italy*

Abstract

Analyses in the plant field have to cover a wide range of topics, starting from metabolomics to the quali-quantitative determination of a single or a class of metabolites, often dealing with very complex matrices. The development of an appropriate sample preparation method is fundamental to obtain complete information, because downstream analyses will detect only the metabolites previously extracted. The choice of the proper extraction phase is therefore of utmost importance and the most critical parameter to be considered. Although most of the studies on plants still mainly adopt traditional extraction techniques, a wide number of new phases with improved features in terms of tunability, selectivity and, most important, sustainability have been developed in the past decades and applied to the study of natural products. This review provides an overview of the new extraction phases developed and adopted for the study of plant endogenous and exogenous metabolites.

[§] Both authors contributed equally to this work

*Corresponding author: cecilia.cagliero@unito.it, Via Pietro Giuria, 9, I-10125, Torino, Italy, Tel: +39-011-6707133

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Abbreviations: ABS: aqueous biphasic system, **Bio-IL:** bio-renewable IL, **CD**: cyclodextrin, **ChCl**: choline chloride , **CNT**: carbon nanotube, **COF**: covalent-organic framework, **DES**: deep eutectic solvent, **DI**: direct immersion, **DLLME**: dispersive liquid-liquid microextraction,

FT-IR: Fourier transform infrared spectroscopy, **GO**: graphene oxide, **rGO**: reduced graphene oxide, **HBA**: hydrogen bond acceptor, **HBD**: hydrogen bond donor, **IL**: ionic liquid, **HS**: headspace, **IL-HIM**: ionic liquid−hybrid molecularly imprinted material, **ILMHDE**: IL-mediated microwave-assisted hydro distillation liquid-liquid extraction, **ILUMASDE**: ionic liquid-based ultrasound/microwave-assisted simultaneous distillation extraction, **MAE**: microwave assisted extraction, **MCE**: mechanochemical extraction, **MNP**: magnetic nanoparticle, **MIL**: magnetic ionic liquid, **MIP**: molecular imprinted polymer, **MOF**: metal organic framework, **MSPD**: matrix solid phase dispersion **MWCNT**: multiwalled carbon nanotube, **NADES**: natural deep eutectic solvent, **PANI**: polyaniline, **PCB**: polychlorobiphenyl, **PDMS**: polydimethylsiloxane, **PIL**: polymeric ionic liquid, **PPy**: polypyrrole, **PSA**: primary-secondary amine, **PVC**: polyvinyl chloride, **QuEChERS:** Quick, Easy, Cheap, Effective, Rugged, and Safe, **UAE**: ultrasound assisted extraction, **SLE**: solid-liquid extraction, **SPME**: solid phase microextraction, **SPE**: solid phase extraction, **dSPE**: dispersive SPE , **µ-dSPE**: miniaturized version of dispersive SPE , **m-SPE**: magnetic solid phase extraction, **ToF**: time of flight , **TRIL**: temperature-responsive hydrophobic ionic liquid, **UCTS**: upper critical solution temperature, **UHPLC**: ultra-high performance liquid chromatography.

1. Introduction

Natural product analyses must cover a wide range of topics, starting from the study of plant metabolomes to the quality control and determination of endogenous and exogenous compounds. In both cases, sample preparation plays a fundamental role. In fact, all plant metabolites should be extracted in metabolomics studies. However, a universal extraction phase or technique is practically impossible to find because of the complexity of plant systems and the chemical diversity of metabolites [1]. On the other hand, the determination of single or multiple metabolites, which are often present at trace levels in plant materials, is required in quality control analyses. The analytical challenge here is the development of methods that can detect target compound(s) at low limits, as often required by regulations, meaning that proper enrichment is required [2].

The development of appropriate sample preparation methods in the plant field faces particular challenges as the complexity of plant biological systems can affect the reliable determination of target analytes. In fact, the metabolome of a plant comprises a high variety of compounds, ranging from different classes of primary metabolites (sugars, proteins, fats and nucleic acids) to a very wide range of specialized metabolites (such as terpenoids, alkaloids, phenolic compounds and others). Another issue in plant analysis is the presence of chlorophylls and other pigments; these molecules are present in high amounts in the photosynthetic parts of the plant, but poorly compatible with downstream analyses, and with HPLC systems in particular, because of their strong interaction with commonly used reverse stationary phases. At the same time, it is important to remember that plant cells are protected by thick and robust lignocellulosic walls that should be disrupted if the efficient extraction of intracellular metabolites is to be achieved.

A number of mechanical means, including ultrasound and microwaves, can be adopted to increase the efficiency of metabolite extraction. However, the choice of the appropriate extraction phase is of utmost importance, and is the most critical parameter to be considered. The extraction phase should either cover the widest possible array of metabolites in metabolomics studies, or increase the selectivity and the enrichment of target analytes in studies dealing with the determination of specific compounds.

In this sense, most studies on plants still principally adopt traditional extraction techniques, including liquid-liquid extraction and Soxhlet extraction, that entail the high consumption of toxic organic solvents. However, the use of miniaturizing techniques and, in particular, of new classes of more sustainable extraction phases is gaining ground as they meet the criteria of Green Analytical Chemistry [3]. Furthermore, these techniques can be tailored to increase extraction selectivity towards specific compounds [4,5].

This review aims to provide an overview of the extraction phases that have been developed and adopted, over the last three years (from 2017 to 2020), for the study of endogenous and exogenous plant metabolites. A critical evaluation of the main features of each phase will be provided as well as some ideas for new applications in the plant field (see also figure 1 and table 1).

The first part of this review deals with the evaluation of new green extraction solvents (ionic liquids and deep eutectic solvents) in the liquid-phase extraction of natural products, while the second part is devoted to the evaluation of innovative solid sorbents for the clean-up and pre-concentration of plant extracts. The potential, limits and future trends of each extraction phase will be highlighted in both cases.

2. Liquid extraction phases

The choice of extraction solvent is of utmost importance when dealing with the extraction of plant metabolites, and the search for new green solvents has become one of the most significant subjects in the sample preparation field. In this respect, ionic liquids (ILs) have received a great deal of attention as they may be able to replace organic solvents in the extraction of natural products. Moreover, deep eutectic solvents (DESs) are also gaining position in the field of plant sample preparation. In fact, these "green" solvents can be combined with a range of extraction techniques, such as ultrasound assisted extraction (UAE) and microwave-assisted extraction (MAE), and can be exploited in liquid-phase microextractions.

In this section, the potential of using ILs and DESs as liquid extraction phases in the plant field will be presented and critically discussed together with their possible weaknesses. Figure 1b provides a representation of the structure of the liquid extraction phases that have been investigated, while table 2 reports a number of representative applications.

2.1 Ionic Liquids

Ionic liquids (ILs) are an interesting class of molten salts whose physicochemical properties have inspired the rapid development of new applications in analytical chemistry and, in particular, in the sample-preparation field [6]. They are organic salts that possess melting points at or below 100 °C. In most cases, they are composed of an organic cation and an organic or inorganic anion, and are characterized by high thermal stability, low vapor pressure and varying viscosity, conductivity and miscibility in different solvents.

One of the main features of ILs, compared to traditional organic solvents, is their ability to incorporate functional groups, within the IL structure, that selectively interact with specific analytes or a class of analytes. The chemical structure of ILs (type of functional groups and/or anion/cation combination) can be tailored to provide various solvation interactions (such as hydrogen bonding, electrostatic, hydrophobic and $\pi-\pi$ interactions) and capabilities with both polar and apolar compounds, thus giving ILs with very different properties in terms of water solubility and solution behavior [6,7]. In addition, since they present negligible vapor pressure at room temperature, they prevent solvent loss to the atmosphere and decrease the environmental footprint, thus making them a sustainable alternative to organic solvents.

Many studies have also demonstrated the ability of ionic liquids to dissolve cellulose and other cell-wall components (such as hemicellulose and lignin), via the decrystallization of the cellulose portion of lignocellulosic biomass, and simultaneously disruption of the lignin and hemicellulose network [8,9]. In fact, the anions of ionic liquids can form strong hydrogen bonds with the hydroxyl groups of cellulose, and thus eliminate their intramolecular hydrogen bonds and disrupt cell walls, causing cell lysis. This ability can be exploited for the pre-treatment of plant material before its extraction, for instance before or during hydrodistillation, at laboratory scale, to increase essential oil yield [10,11].

The above-mentioned properties have allowed ILs to find many applications as solvents in extraction and separation processes for bioactive compounds, either in simple solid-liquid extractions (SLE) or in microwave-assisted (MA) and ultrasound-assisted (UA) extractions [5,12]. In particular, because of their high polarity and high thermal stability, ILs are heated rapidly and uniformly under microwave irradiation being considered as excellent microwave absorbers. They can also be used in UAE, in particular for extracting thermolabile compounds in short times and at room temperature [5].

Because of their versatility, ILs can be adopted in liquid-phase extractions of natural products under different extraction modes. They can be used as surfactants above their critical micellar concentration, as reported by Mastellone *et al.* in a study that exploited 1-hexadecyl-3-butyl imidazolium bromide as IL surfactant for the extraction of phenolic compounds from *Vitis vinifera* L. leaves [13], and in another work by Moučková *et al.* that evaluated a set of structurally different IL-based surfactants for the flavonoid profile determination of *Mangifera* spp. and *Passiflora* spp. leaves [14]. They can also form aqueous biphasic systems (ABS) when the aqueous IL solution is mixed with inorganic salts that promote phase separation and increase analyte(s) enrichment. This approach has been adopted, for instance, for the extraction of eight ginsenosides from the flower buds of *Panax ginseng* C.A.Mey; in this study, the extraction of the analytes has been carried out by aqueous IL-based UAE and it has been followed by the separation of the IL phase with an ABS, using NaH_2PO_4, and by the direct analysis by HPLC-UV [15]. Finally, dispersive liquid-liquid microextraction (DLLME) can be used when dealing with liquid samples, such as herbal teas. In this case, hydrophobic ILs are dispersed in the water solution with the aid of a dispersive solvent and the IL-phase is recovered and analyzed. In the IL-DLLME procedure, ultrasound energy can be applied to accelerate the mass transfer process and to improve the extraction efficiency. In addition, the solubility of target analytes in ILs can be optimized by changing the temperature. An ultrasonic-assisted temperature-controlled IL-DLLME approach has recently been coupled to HPLC-UV and applied for the determination of pyrethroid residues in herbal teas [16].

ILs can also incorporate a paramagnetic element into their structure, either in the cation or in the anion giving rise to the magnetic ionic liquids (MILs), a sub-class of ILs whose application in sample preparation is rapidly increasing [6,7]. MILs have found some applications in the plant field, in particular in the extraction of sinomenine from *Sinomenium acutum* (Thunb.) Rehder & E.H.Wilson [17] and in the extraction, adopting an ABS approach, of berberine from the rhizome of *Coptis* spp [18]. They also have been used for the isolation of DNA from *Arabidopsis thaliana* (L.) Heynh. and other plants [19]. These compounds have great potential for the extraction of endogenous and exogenous metabolites from vegetable matrices because they combine all of the features of ILs with the ability to exploit their paramagnetic characteristics that allow them to be easily separated using an external magnetic field, in a very rapid process that avoids centrifugation and filtration steps. MILs therefore deserve to be taken into more serious consideration when the extraction phase for the sample preparation of plant matrices is selected.

ILs can also be incorporated in solid phase platforms, either alone (as polymeric ionic liquids, PILs) or in combination with other sorbents to form composites. PILs are polyelectrolytes obtained through the polymerization of IL monomers. PILs not only retain the main features of ILs, but also present the inherent properties of polymers with enhanced mechanical stability and conductivity properties. Thus, they are the best option to exploit the outstanding properties of ILs in sorbent-based microextraction strategies. For instance, they can be used in solid phase microextraction (SPME) as sorbent coatings directly bonded and crosslinked to rugged supports. PIL-based SPME fibers can be applied in both direct immersion (DI) and headspace (HS) extraction modes and can be coupled to both HPLC and GC analysis. For instance, PIL coatings have found use in the determination of acrylamide in brewed coffee and coffee powder by DI-SPME [20,21] and in the profiling of the volatile compounds from *Echinacea* spp. flowers by HS-SPME [22], in both cases coupled to GC-MS analysis.

In addition, a number of IL-based composites have been developed to exploit the unique properties of ILs in sorbent-based strategies, such as in solid-phase extraction (SPE) [23]. In the plant field, for instance, a bionic multi-tentacled ionic liquid-modified silica gel has been synthesized and used as a selective adsorbent in the separation of tea polyphenols from green tea [24]. Ionic liquids and β-cyclodextrin functionalized magnetic graphene oxide materials have been synthesized for the extraction of plant growth regulators in vegetable samples that were pre-extracted with 1% acetic acid in acetonitrile [25]. ILs have also been widely employed in combination with natural sorbents, molecular imprinted polymers (MIPs) and carbon-based materials; these composites will be better described in section 3.

Thanks to the tunability of their structure and, consequently, of their properties, ILs can be applied to both metabolomics studies and the selective extraction of specific endogenous and exogenous compounds. When dealing with metabolomics studies, ILs can be exploited for the simultaneous determination of volatile and non-volatile components [26-28]. Different approaches for the determination of these classes of compounds in plant matrices have recently been developed. In the first case, an efficient IL-mediated microwave-assisted hydrodistillation has been concatenated with liquid-liquid extraction (ILMHDE) for the distillation of essential oil and the simultaneous extraction of a set of non-volatile flavonoids (astragalin, quercetin, luteolin, kaempferol and apigenin) from the inflorescences of *Helichrysum arenarium* (L.) Moench. An IL solution is added to the plant material and submitted to microwave-assisted hydrodistillation, and the hydrosol is then collected in two separation columns, the first of which recovers the volatile components, while the second collects the non-volatile compounds after the addition of an organic solvent. [27]. ILs can also be used in combination with enzyme digestion, as clearly shown in a study in which a solution of 1-butyl-3-methylimidazolium bromide and a mixture of cellulase and pectinase have been used as pretreatment before the simultaneous extraction, through a modified hydrodistillation concatenated Soxhlet extraction apparatus, of procyanidins and essential oil from the pinecones of *Pinus koraiensis* Siebold & Zucc. [28]. Finally, an ionic liquid-based ultrasound/microwave-assisted simultaneous distillation extraction (ILUMASDE) approach can be used. Again, an IL-water solution is added to the plant material and submitted to UAE and/or MAE but, in this case, the non-volatile components are directly determined in the solvent solution, while the volatile components are collected after the condensation of the vapor phase. This approach has been successfully applied to the determination of the flavonoids and volatile components in sea buckthorn (*Elaeagnus rhamnoides* (L) A. Nelson) leaves, and has provided a drastic reduction in extraction times, higher analyte recovery and similar volatile composition, compared to conventional hydrodistillation. [26]. The ability to extract hydrophilic and hydrophobic non-volatile compounds at the same time is also very interesting. For instance, an ionic-liquid-based ultrasonic-assisted extraction has been used to simultaneously extract gingerols and polysaccharides from ginger (*Zingiber officinale* Roscoe) with higher yields and reduced extraction times for both classes of compound [29]. The use of temperature-responsive hydrophobic ionic liquids (TRILs) for the simultaneous extraction of hydrophilic and hydrophobic compounds, followed by their separation and pre-concentration at lower temperatures, is another remarkable alternative. In fact, TRILs are soluble in water above a certain temperature (the upper critical solution temperature, UCST) and immiscible below the UCST. As illustrated in figure 2b, the extraction process is carried out at high temperature, exploiting the different polarities of the two solvents, and then the *in-situ* separation and pre-concentration of the target compounds is achieved by reducing the temperature below the UCST, meaning that the extraction solvent will switch from being single-phase to two-phase. This approach has been developed specifically for the extraction of bioactive compounds from medicinal plants, and has been applied to *Chrysanthemum* spp., as a case study [30].

On the other hand, the structure of ILs can be tuned for the selective recovery of plant metabolites belonging to specific chemical classes As previously mentioned, a cholinium-based MIL has been exploited for the selective extraction of berberine from the rhizome of *Coptis* spp [18] but numerous other examples can be found in literature, as reported in a recent review by Xiao et al [31]. Furthermore, ILs can be exploited for the selective extraction and pre-concentration of toxic exogenous compounds. As already reported, an IL-based SPME and an IL-based *in-situ* DLLME method have been developed for the extraction of acrylamide from coffee [20,21,32] and an IL-based DLLME approach has been adopted for the selective extraction and determination of pyrethroid residues in herbal teas [16].

Despite the undoubted advantages of IL-based extractions, these molecules also have some limits. One drawback is the difficulty in recovering extracted compounds because of the negligible vapor pressure of ILs. This limit mostly affects their use in the isolation of natural compounds, and less their analytical application. However, the poor volatility of ILs also means that they are not directly compatible with LC-MS analyses or the direct injection into a GC system; as a result, a back-extraction of the analytes from the IL phase is required before their analysis, when these techniques are adopted. The difficulty in recycling and recovering ILs on an industrial scale is also a critical issue.

In addition, although they were originally considered to be green chemicals, some concerns about the toxicity and potential environmental impact of ILs has started to arise in recent years. In fact, most of them are obtained from fossil sources and show poor degradability. In this respect, the current trend is to design ILs to be more degradable and less toxic. In particular, ILs with fluorine-free anions and with more biodegradable cations (e.g. pyridinium or guanidinium) have been developed, in part thanks to the fact that shorter IL side chains in any of the moieties give less toxic ILs. More eco-friendly guanidinium-based ILs have been applied, for instance, in the above-mentioned extraction of flavonoids from *Mangifera* spp. and *Passiflora* spp. leaves [14]. These derivatives, although more environmentally sustainable, still require a large amount of non-renewable solvents in their synthesis, meaning that the use of anionic or cationic counterparts that are fully or partly derived from natural compounds would therefore be an ideal and sustainable approach to the development of a new generation of bio-renewable ILs. (Bio-ILs) [33]. For instance, matrinium-based ionic liquids, derived from the alkaloid matrine, isolated from *Sophora flavescens* Aiton, have optimal physicochemical properties and low cytotoxicity [34]. Unfortunately, these Bio-ILs have rarely been applied in sample preparation and no applications can be found in the plant field. Future advancements in the development of bio-renewable ionic liquids are therefore expected and their application in the extraction of plant matrices should be explored.

2.2. Deep eutectic solvents (DES)

Deep eutectic solvents are systems that are formed by a hydrogen-bond acceptor (HBA) and a hydrogen-bond donor (HBD). As the term "eutectic" suggests, they are characterized by a lower melting point than the individual components. They are usually associated with ILs because they have similar physicochemical properties, including low vapor pressure, low flammability and thermal stability. However, DES can be prepared by incorporating ionic or neutral species, unlike ILs (see paragraph 2.1). Moreover, DESs overcome some of the limits of ILs due to their easy preparation, the low cost of their synthetic raw materials, as well as their lower toxicity and higher biodegradability [35–38]. Since their introduction by Abbot and colleagues in 2003 [39], they have gained popularity in the extraction field thanks to the extraction capacities they present, which are related to H-bonding interactions, polarity and viscosity. The large number of HBAs and HBDs that are available for the preparation of DESs allows many combinations of eutectic mixtures to be easily obtained with different types of extraction performance and characteristics that are suitable for a range of matrices.

In this sense, DESs have been widely explored as valid alternatives to organic solvents for the extraction of bioactive compounds from different plant materials, with a focus on non-volatile endogenous compounds [40]. Of the various components that can be used to obtain a DES, HBAs and HBDs of natural origin, such as amines, sugars, carboxylic acids and polyalcohols, are an attractive source for the preparation of biodegradable and biocompatible DES. These natural deep eutectic solvents (NADES) have found promising applications in the plant field, according to current trends towards the use of green solvents [36,38,41–45]. The solubility of most natural compounds in NADES, which is due to multiple types of interactions including hydrogen bonding, dispersion forces and electrostatic interactions [35], can be explained by a hypothesis developed by Choi *et al.* [46] who proposed that NADES are naturally present in plant cells and act as a third liquid phase in living organisms. In fact, they observed that some primary metabolites (sugars, organic acids and bases, amino acids) naturally occur in similarly high molar ratios in the plant cells, thus probably explaining the multistep biosynthesis of non-water-soluble compounds. In addition, several studies have demonstrated the ability of DESs to cleave lignin-carbohydrate complexes by disrupting covalent linkages and hydrogen bonding, thus affecting the structure of the cell wall and accelerating the release of the compounds [35].

The heating and stirring method is the most common of the procedures employed to prepare DES for the analysis of plants. It normally requires the mixing of two or three components under magnetic stirring, and keeping the temperature at 40-90°C until a homogeneous liquid is produced. [36,38,41–44,47]. When preparing a DES, it is important that hydrogen bonds are formed between the two components (HBA and HBD), and an FT-IR spectrum of the mixture can therefore be a useful tool to evaluate their correct formation [42,47]. Moreover, the DES instability over time can lead to the formation of crystals in the mixture, and a visual inspection is a simple way to evaluate whether the correct procedure and HBA/HBD ratio were used to obtain a stable preparation. For instance, Kaltsa *et al.* [44] have examined several lactic-acid-based DESs for the presence of crystals, at regular intervals over 6 weeks. A range of different physicochemical properties were observed according to the HBA and HBD chosen, and the ratio used. For example, the widely used HBA choline chloride (ChCl) can be combined with polyols (e.g. ethylene glycol, glycerol…), carboxylic acids, amides, alcohols, sugars and amino acids to give mixtures with different polarities and viscosities [36,38,42,43]. As a result, the higher viscosity of sugar-based DES (e.g Choline chloride-D-glucose) led to a lower extraction capacity for flavonoid glycosides and aglycones from the Chinese herbal medicine Platycladi Cacumen (*Platycladus orientalis* (L.) Franco), compared to other DESs [43]. Viscosity is a key point when dealing with DES because it can affect the mass transfer of analytes during extraction. The main ways of reducing viscosity include higher extraction temperatures, which may result in the degradation of the target compounds if not properly controlled, and the addition of water [43]. The presence of water clearly affects the polarity of the solvent. Consequently, it is not surprising that glycosides are more influenced by water content than aglycones, even though the extraction of the more hydrophilic glycosides does not improve with higher percentages of water. In fact, the correlation between analyte solubility and water content is not linear, and the careful optimization of this parameter is fundamental to achieve good performance, also considering that the presence of water may also interfere with the formation of the hydrogen bonding network [35,41].

Ultrasounds [28,30,33,35,36,38,39] or microwaves [36] are often employed during an extraction to enhance the transfer of analytes from the vegetal matrix to the eutectic solvent, resulting in a greener approach due to the decrease of extraction time and energy consumption [5]. However, prolonged or excessive heating are generally not recommended as they can lead to the degradation of thermally unstable analytes, and also of some HBDs and HBAs [35]. Yao *et al.* have compared the performance of heat-stirring, microwave and ultrasound extraction in the analysis of phenol compounds from *Pyrola asarifolia* subsp. *incarnata* (DC.) Haber & Hir. Takah*,* and microwave-assisted extraction led to better results thanks to its fast and focused heating [36].

A further aspect in the use of DES, that meets the Green Chemistry principles, is the absence of harmful organic solvents, both in the synthesis of DES and during the extraction process, unlike other sorbent-assisted extractions (e.g MWCNTs, MOFs…). This is a key point in the plant field. As previously mentioned, the complex composition of vegetal materials, including the presence of pigments (e.g. chlorophyll), usually means that a pre-treatment process is needed to eliminate these interferences, and large quantities of harmful organic solvents, such as MeOH, EtOH, acetone and hexane, are consumed. On the contrary, the common procedure with DES involves a solid-liquid extraction of the dried plant at 25-70°C in hydrophilic media. The percentage of water added to the eutectic mixture prevent the transfer of chlorophyll and other apolar interferences from the plant material to the extract [36,43,44,47,49]. However, it is important to highlight that a certain volume of solvent is normally used to dilute the sample before the analysis, this step is necessary to decrease the viscosity of the final extract in order to prevent damage to the chromatographic system [38,41,43,47,49]. Nevertheless, as discussed for ILs, the direct injection of the DESs in the chromatographic system when LC is coupled to MS is not possible because of their low volatility. The recovery of the target analytes from the eutectic mixture is therefore mandatory for LC-MS analyses. This latter involves the use of macroporous resins [41,43,50] or antisolvents that disrupt the hydrogen bonding between the two components of the DES [35,40]. In this sense, Fu *et al.* [42] performed a purification step by solid phase extraction (SPE) using a DES-modified adsorbent and a ChCl-based DES for the elution of polyphenols from palm bark samples (*Trachycarpus fortunei* (Hook.) H.Wendl), obtaining an enrichment of the analytes without using organic solvents and expensive SPE phases. Moreover, the same volume of DES and water was eluted through the SPE column, achieving a proper dilution of the final extract.

As previously mentioned, DESs have found many applications in the plant field, mainly because of their ability to extract a very wide range of compounds. In particular, they have been extensively applied for the extraction of phenolic compounds that have been shown to dissolve better in DESs than in lipids or water [51]. Aside from phenolic compounds, other plant specialized metabolites have been extracted using DES. In particular, Duan *et al.* [38] have thoroughly investigated the behavior of several DES species in the extraction of various bioactive compounds, including alkaloids, saponins and anthraquinones. For the alkaloids, carboxylic acid-based DES (e.g. betaine laevulinic acid) resulted to be a more efficient solvent, than MeOH, less suitable for extracting partially ionized compounds. On the other hand, acid-based DESs are not suitable for the extraction of saponins, and better results were obtained when using dimethylurea or methylurea as HBD. Finally, anthraquinones were poorly extracted by the majority of the hydrophilic DES as a result of the low polarity of these compounds. In general, the study demonstrated that sugar- and alcohol-based DESs had a lower extraction capacity than MeOH towards low-polarity analytes. In this respect, hydrophobic DESs can be used to extend the application of these solvents to the analysis of poorly polar compounds as the properties of DESs can be tailored as a function of HBA and HBD structure. For instance, a HBA consisting of methyl trioctyl ammonium chloride combined with 1-propanol in a 1:4 ratio has been successfully applied for the extraction of artemisin, which is an apolar terpenoid used in malaria treatment, from *Artemisia annua* L. [52]. A new generation of hydrophobic NADES has also recently been developed by mixing menthol with different HBDs [53]. The combination of menthol and 1-propanol has been used for the isolation of taxanes from *Taxus wallichiana* var. *chinensis* (Pilg.) Florin (syn. *Taxus chinensis*

(Pilg.) Rehder)needles, and was found to be more efficient than conventional solvents, such as MeOH or EtOH [47]. Despite the apolar nature of taxanes, the DES with 80% water content showed better extraction efficiency than a common hydroalcoholic solvent. It could also boast of less solvent consumption, confirming that the presence of water plays a critical role when using DES. The same HBA has been combined with different carboxylic acids in an efficient extraction of four cannabinoids from *Cannabis sativa* L. inflorescences. [48]. It is interesting to highlight that the extraction yield was not only affected by the viscosity of the mixture, but also by the different alkyl chain lengths of the HBD used, which may have improved interactions with more lipophilic compounds. NADESs (together with ILs) have also been investigated in the extraction of ecdysteroids, and, in particular, 20-hydroxyecdysone, from spinach (*Spinacia oleracea* L.) and several advantages were found, including higher selectivity, simplicity, efficiency, and rapidity, as well as the recovery and much lower consumption of organic solvents, in comparison with conventional methods [54]. In addition, it has been shown that DESs are also able to extract volatile compounds. In fact, the headspace SPME of the DES extracts of peppermint leaves and tobacco powder shows a richer volatile profile than that of conventional methods [55,56].

Very interestingly, DESs are also able to preserve the bioactivity of the compounds. Several studies have demonstrated the ability of DESs to stabilize the antioxidant capacity of natural products [35], as shown, for instance, for the choline chloride-based extract of phenolic compounds from *Rosmarinus officinalis* L., which provided higher antioxidant capacity and lower degradation kinetics than the corresponding ethanolic extract [57]. This feature opens the perspective of the direct use of NADES extracts in the health field. In fact, NADESs composed by HBAs and HBDs that are commonly introduced in our daily diet (such as sugars, amino acids or citric acids) can likely be directly used for food and pharmaceutical purposes [41]. However, current studies rarely investigate the bioactivity, biotoxicity and metabolism of these derivatives. In this sense, Zhao *et al* [58] have tested the biocompatibility and biodegradability of a series of DESs that were used for the extraction of rutin from *Styphnolobium japonicum* (L.) Schott. Bacterial growth inhibition was higher for organic acid-based DES than for alcohol- or sugar-based DES, although the antimicrobial effects of all of the tested DESs were lower than those of some conventional ILs. In addition, the biodegradability level of the organic acid-based DES was the lowest, although its value was still within acceptable limits.

The outstanding features of this innovative class of solvents have led to increasing interest in a number of applications, in particular in the plant field. The psychochemical characteristics and environmentally friendly profile of DES perfectly match the principles of Green Analytical Chemistry, including the replacement of harmful organic solvents, and the natural origin of the majority of the HBAs and HBDs available. At the same time, however, it is important to highlight that there is a need to overcome some drawbacks in their use. These disadvantages are mainly related to their viscosity, which can negatively affect extraction time (up to 2 hours), extraction capacity and compatibility with the main analytical platforms, if not properly controlled. These future challenges may provide the basis for new perspectives in the use of DESs.

3. Solid sorbents

A wide range of new sorbents has recently been developed for sample preparation. Several of them have been applied in the plant field, in particular for the clean-up and pre-concentration of specific analytes from water and organic extracts. In general, they show good potential in terms of efficiency and sustainability. However, it should be noted that plant matrices are commonly solids, as are the sorbents, meaning that previous sample extraction has to be carried out to allow a solid phase extraction with the sorbents. In most cases, it is performed with organic solvents, and this decreases the sustainability of the whole process. However, greener alternatives are available in the form of matrix solid-phase dispersion extraction (MSPD), and via pre-extraction with the green solvents described above.

In this section, the potential of the main classes of solid sorbents that have been exploited in the extraction of natural products will be discussed, together with their main limits and future trends. Figure 1b reports an illustration of the structures of the investigated sorbents and table 2 reports some representative applications.

3.1. Natural sorbents

Natural sorbents are certainly the greenest alternative to conventional materials in extraction procedures, and they comply with the increasing concern about environmental sustainability and safety. Apart from their low ecological impact, these sorbents are cheap, compared with other extraction phases, and easily available from natural sources. They include sorbents with a range of characteristics, but the common principle is the exploitation of natural products as raw materials for the preparation of sustainable and efficient extraction phases. Over the years, many natural sorbents have been demonstrated to possess good extraction capacities together with suitable characteristics for extraction, such as mechanical strength, gelling properties and tunability [59–61].

According to literature, two main classes have been explored as sorbent phases in plant extraction: i) biopolymers; and ii) food by-products. The first are isolated from living organisms and consist of monomeric units (e.g. nucleotides, monosaccharides, amino acids) that are covalently bonded to form a polymeric chain. Polysaccharides have undergone the most widespread explorations in the extraction of endogenous and exogenous compounds from plants. Chitosan and cellulose have been used in different formats, including as dispersants [62–64], SPE cartridges [65,66], nanoparticles [67,68], and fibers [69], thanks to their versatility. Unlike cellulose, which is abundant in the walls of vegetal cells, chitosan is mainly derived from the skeletons of marine animals, as a deacylated form of chitin. Both materials present surfaces that are rich in hydrophilic groups, which can easily form hydrogen bonding and electrostatic interactions with target analytes [59]. Sporopollenin, a major component of the external walls of pollen grains, is another interesting biopolymer. It has gained attention as a sorbent material for its impressive resistance to high temperatures and chemical treatments. However, it has been less thoroughly explored than other [61]. Its adsorption capacity comes from the presence of several different functional structures on its surface, including hydroxylic groups and saturated and unsaturated aliphatic chains with aromatics. In this regard, Qian Lu and colleagues have tested pollen grains as SPE sorbents for the determination of plant growth regulators and *trans* resveratrol in different vegetal samples, and have reported that this biopolymer presents excellent separation and purification properties [70,71].

The use of food by-products as sorbent phases in the extraction of vegetable matrices has been documented in the literature, and some interesting applications have been proposed [72–74]. The valorization of biomass that is normally discharged as food waste is an added value for this type of sorbent in view of the circular economy paradigm. For example, Jiang *et al.* have used crab shells from a local restaurant as the starting materials for a chitosan-rich powder that has been used for the isolation of anthraquinones from *Senna* spp. (syn. *Cassia*) [72]. Food by-products can also be used to obtain carbon-based materials, and thus avoid the use of fossil-fuel based precursors. In two different works, sorbents that were obtained from fruit peels have been able to extract pesticides from vegetal complex samples. Hierarchical porous carbon from banana peel presents a large surface that is rich in graphitized pores, and these pores are capable of selective interactions with the aromatic groups of carbamate pesticides [73]. In a second work, magnetic nanoparticles with a carbon structure have been prepared from the hydrothermal carbonization of pomelo peel, and the FT-IR spectra showed that the surface was rich in oxygen-containing groups [74].

A further point that must be taken into account when attempting to develop a greener extraction approach, is to consider all the step of the procedure, and not only one aspect, such as the sorbent. Thus, the decrease in consumption of toxic solvents and energy, the production of waste and the reusability of the sorbent should all be considered. In this sense, the elimination of use of toxic solvents, which are usually necessary to desorb the analytes, is a true challenge when the extraction phase is a solid sorbent. However, as mentioned before, microextraction techniques can help to reduce solvent consumption or green solvents (e.g. ILs) can be employed as adequate substitutes [72]. An evaluation of the reusability of a sorbent is also an important factor in reducing analysis costs and waste production. In general, many of these natural sorbents can be re-used several times [69,70,74]. However, Li *et al*. [68] have observed that their cellulose-MIP microspheres showed reduced adsorption capacity, by more than 10%, after five cycles of extraction. This may have been due to a loss in adsorption cavitation during the adsorption-desorption process. On the other hand, the performance of graphene oxide functionalized cotton fibers was found to be almost unaltered after 50 extraction procedures, and the regeneration process only entailed sonication in a MeOH/ACN solution for 5 minutes [69].

The use of natural sorbent as such should be preferable in order to develop green methods, simplify the process and reduce the number of tedious synthetic steps that are normally required when numerous phases are involved. In many examples, natural materials exhibit excellent extraction capacities thanks to their specific functional groups and porous structures, which allow proper interactions with the target analytes without further functionalization [62–64,66,70,73]. On the other hand, the functionalization and/or combination of different sorption mechanisms can enhance extraction performance, and a number of works have developed hybrid phases starting from natural sorbents. For example, the incorporation of magnetic particles into a sorbent material is a well-known method with which to simplify extraction procedures. In this way, the sorbent can be easily collected from the plant sample with a magnet, and thus further separation steps are avoided [67,68,74,75]. Some interesting applications have combined solid-phase extraction with IL-based extraction for a range of different purposes. The liquid phase can act as a green solvent for the elution of analytes from a natural sorbent [72] or in a pre-extraction step, followed by extraction with the sorbent [67]. In this latter case, the comparison with an organic solvent extraction and the only ionic-liquid extraction without sorbent enrichment, clearly showed that the IL-chitosan combination had a higher capacity for the extraction of natural pigments from the rhizomes of *Curcuma longa L.*

Various extraction techniques have been developed for the isolation of compounds from plant samples, and the versatility of these natural materials can grant significant advantages. Several SPE cartridges have been prepared with chitosan [65], pollen [70] cotton [69] and treated food by-products [73], with these being simply packed into a cartridge and the compounds of interest eluted with a suitable organic solvent. Matrix solid-phase dispersion (MSPD) is an extraction method in which a sample is directly ground and mixed with a solid-phase sorbent and the analytes are subsequently isolated, via adsorption onto a SPE cartridge, and eluted with a certain volume of solvent. One of the main advantages of MSPD is its ability to directly extract solid materials, which is particularly important for plant samples that normally require pre-treatment before extraction. As shown in figure 2e, cellulose and chitosan can act as optimal dispersants and sorbents in MSPD, and have been successfully employed for the extraction of phenols [63] triterpenoid acids [62], anthraquinones [72] and caffeoylquinic acid derivatives [64] from various vegetal samples. Er *et al.* [75] and Xu *et al.* [67] have coupled natural sorbents with a miniaturized version of magnetic dispersive SPE (m-µ-dSPE) to develop a truly sustainable procedure. The method only required a small amount of chitosan nanoparticles, which were dispersed into the liquid sample, and a few microliters of organic solvent to elute the compounds from the sorbent.

These natural materials have been designed to improve the environmental friendliness of extraction approaches, but also to enhance the performance of analytical procedures. Comparisons with common approaches have shown similar or better results in terms of sample and solvent amount, extraction time, LOD and RSD in many examples [62,66,67,72–74].

3.2. Molecular imprinted polymers (MIPs)

Molecular imprinted polymers (MIPs) are a peculiar group of extraction materials with unique “mimic molecular recognition” properties. Interestingly, an interaction site with high affinity for a chosen template is formed during the synthesis of this polymeric matrix. The high selectivity of MIPs is therefore based on the geometry of this cavity and on the presence of specific functional groups that are complementary to the target analyte [76,77].

Regarding extraction in the plant field, MIPs are arising as a valid approach when the goal is to isolate target compounds from the rich phyto-complexes that are typical in plants. Indeed, most extraction phases lack high selectivity for a specific analyte or class of compounds, meaning that pretreatment and/or purification steps for analyte enrichment are usually necessary before extraction. The isolation of exogenous compounds (e.g. antibiotics, pollutants and toxins) from food or environmental samples is one of the most highly developed applications of MIPs in analytical chemistry [77–79]. The use of MIPs in plant analyses follows a different trend, that is the extraction of endogenous bioactive compounds, including molecules with widely differing chemical structures, thanks to the possibility of obtaining tailor-made MIPs [80–86].

When a new material is prepared, an accurate characterization of its morphology (e.g. using scanning electron microscopy, IR spectra) is necessary to verify that the synthesis has occurred correctly. This is especially true with MIPs, since the synthetic protocol involves several reagents and steps. In particular, a monomer interacts with the template (i.e. molecule with the same or similar chemical features as the target analytes) to form the specific cavity that characterizes every MIP. An initiator induces the polymerase chain reaction, while the porogen assures the formation of pores that facilitate interaction with the target analyte during extraction. Finally, a cross-linker ensures the formation of a rigid structure, which must be preserved after the removal of the template, at the end of the polymerization process. Normally, MIPs with different composition/ratio for each component are prepared to find the optimal procedure. The choice of the reagents to use (especially the monomer) clearly depends on the template, and therefore on the target compound to be analyzed. For example, coumarins were easily able to form hydrogen-bonding and ionic interactions with carboxylic groups when methacrylic acid was tested as a functional monomer [80]. Also, the correct selection of the porogen solvent seems to play a key role in the recognition ability of MIPs, and can directly influence their morphology. In this respect, chloroform, acetonitrile and toluene have been documented to be the most effective [80,82,83]. Moreover, many polymerization techniques have been developed over the years, including emulsion, precipitation and bulk polymerization, which is the most commonly used [76,78,79]. According to *Gao* et al., the precipitation method is the most suitable for the synthesis of spherical nano/microparticles and has been successfully applied in the preparation of nanosized-MIPs, for the extraction of tiliroside from *Edgeworthia gardneri* (Wall.) Meisn [82]. Ionic liquids can be used as porogenic solvents when preparing MIPs as they form discrete polar and non-polar microenvironments that lead to an enhanced interaction between the template and functional monomer, and limit nonspecific binding. In addition, ILs have been shown to accelerate polymerization and improve the effect of imprinting. This strategy has been applied for the isolation of corilagin, a bioactive ellagitannin, from a *Phyllanthus urinaria* L. water extract: corilagin-MIP monoliths were prepared using 4-vinylpyridine as a functional monomer, and ethylene glycol dimethacrylate as the cross-linking monomer, using a mixture of 1-butyl-3-methylimidazoliumtetrafluoroborate (ionic liquid) and N,N-dimethylformamide-dimethyl sulfoxide as a porogen [87]. Ionic liquids can also be used in combination with MIPs to form hybrid materials that combine the selectivity of MIPs with the ion-exchanging and electrostatic-attraction ability of ionic liquids. An IL−hybrid molecularly imprinted material (IL-HIM) has, in fact, been used as a sorbent for the solid-phase extraction of two plant-growth regulators, namely 6-benzyladenine (6-BA) and 4-chlorophenoxyacetic acid (4-CPA) from bean sprouts, coupled to HPLC analysis. The hybrid material is suitable for the simultaneous determination of the two target analytes in bean sprouts, but accurate selectivity and competitive experiments showed that the adsorption of 6-BA onto IL−HIM is based on selective imprinted recognition, whereas the adsorption of 4-CPA is mainly dependent on ion-exchange interactions [88].

While MIPs have mostly been associated with SPE, the primary goal in their use is currently the incorporation of miniaturized extraction techniques to improve the accuracy and precision of the method and, at the same time, decrease sample and sorbent consumption [89]. However, the combination of MIPs and microextraction methods in the plant field has yet to be thoroughly investigated. Some SPME coatings have recently been developed and successfully used for the enrichment of low concentration bioactive compounds, such as auxins [83] and for the rapid detection of the potentially toxic pyrrolizidine alkaloids [86]. In the first example, a pre-treated silica fiber was inserted into a prepolymer solution of the MIP, and the glass tube was transferred to an oven at 60°C for 8 hours for the polymerization step. It was reported that the porogen affected the thickness of the coating, and therefore the adsorption capacity. In particular, the authors observed that the repetition of the polymerization cycle on the same fiber for up to five times assured the maximum extraction rate by increasing the binding sites on the fiber. Moreover, the MIP coating had good chemical stability, which was demonstrated by immersing the fiber in different organic solvents for a couple of hours. A different approach was employed for the preparation of the pyrrolizidine alkaloid-MIP, where the quarts fiber was first treated with the template and the monomer, while the crosslinker was added subsequently. In this case, monocrotaline was chosen as the dummy template to simulate the alkaloid structure as the standard materials for these latter structures are quite expensive. Most importantly, if the template is not properly eliminated it can be released during extraction, causing false positive results in the sample. For this reason, the use of the target analyte as template should be carefully handled. Both of the SPME-MIP applications showed high selectivity for the selected analytes and better sensitivity, in terms of LOD, than conventional extraction techniques.

A further application for MIPs as electrochemical sensors, which find some applications in plant analysis, is worth mentioning. Again, several procedures have been used to prepare the MIP-functionalized electrodes. Alipour *et al.* have prepared a sensor that is based on magnetic MIPs for the determination of rosmarinic acid from four plant extracts (*Salvia officinalis* L.*, Zataria multiflora* Boiss.*, Mentha longifolia* (L.) L.*,* and *Rosmarinus officinalis* L.). The magnetic MIP has been mixed with graphene powder to obtain a carbon electrode. The magnetic component improves the kinetic rate of electron transfer, while the MIP increase the selectivity of the system for the target analyte. The plant material has been treated with different organic solvents before the analysis and the voltammograms has been recorded at 0.0-0.35 V [84]. Yang and colleagues used the same principle to prepare a portable and cheap sensor for the rapid determination of gallic acid in edible plants. In this case, MIP-based sensor has been placed in a PVC tube and insert in an aqueous solution of the sample, as represented in figure 2d [85]. pH dependency was investigated in both examples as it has an influence on the electrochemical behavior of the molecules. Indeed, very acidic pH values reduced the carboxylic ionization of gallic acid, while the upper pH range led to the degradation of the compound.

Apart from selectivity, versatility is one of the main advantages of MIPs. Their characteristics, including durability over a wide range of pH values and temperatures, make them suitable for innovative applications as extraction phases. A recent review by Arabi *et al.* gives a comprehensive overview of the new trends in MIP-based SPE, including nano-scale MIPs, composite MIPs, hollow porous MIPs and many others [78]. Again, the application of these novelties in plant field have been less frequently explored compared to other application fields. However, progress on this is being made. The preparation of surface-imprinting MIPs that are based on boron nitride and deep eutectic solvents for the isolation of flavonoids, and that give a high specific surface area of extraction is an interesting example [90].

Although MIPs show outstanding features, there are still some critical points. Current and future effort will undoubtedly be directed towards the improvement of these aspects. In particular, the synthesis of MIPs requires many steps and reagents, including high amounts of toxic solvents to remove the template. The incorporation of green materials/solvents should be considered as a means to avoid the large-scale consumption of hazardous substances. The synthesis of water-compatible MIPs is another hot topic, because the presence of water can negatively affect non-covalent binding with the analyte, decreasing interactions with it [77]. However, some water-compatible MIPs, that can be directly used in aqueous media, have been developed. These phases are particularly important in the plant field as vegetal matrices are normally pre-treated with polar solvents to give hydrophilic extracts. Finally, the high selectivity of MIPs can be unfavorable when the goal is to isolate a class of compounds and not a single analyte. Again, this is particularly true for plant extraction, in which specialized metabolites are numerous and heterogeneous. Moreover, compounds from the same chemical class can present quite different functional groups in their structure, and molecules with low similarity to the template may have some difficulties interacting with MIP cavities. To solve these problems, Sun *et al.* have developed an off-line two-dimensional MIP-SPE for the extraction of ellagitannins from pomegranate [81]. In particular, ellagic acid and punicalagin MIP SPE columns were prepared and used as the first and second dimensions, respectively. Different fractions were collected after the elution to study the distribution of the analytes as a function of the purification procedure. Careful optimization of each elution step and elution solvent is needed to obtain good enrichment for each ellagitannin. Moreover, the use of the ellagic tannin MIP as the first dimension is important to improve the capacity and the recovery of the analytes, while using the punicalagin MIP column as the second step allows the non-specific adsorption of the ellagic acid step to be overcome, and good selectivity to be achieved.

Although the “molecular key and lock” theory that is behind the functioning of MIP materials is somewhat dated [91], these extraction phases can be considered valuable and promising tools in the extraction of natural products, especially when coupled with innovative approaches such as miniaturization, green chemistry and automation.

3.3. Magnetic nanoparticles (MNPs)

Metallic materials have also found applications in microextraction in the plant field. They have been used because of their high thermal, mechanical and chemical stability, and feasible functionalization. Of the various nanoparticles to have been developed, those made from transition metals (Fe, Co and Ni), and from their oxides, and, in particular, magnetite (Fe_3O_4), are the most commonly used [92]. Given their superparamagnetic properties, which permit their easy and quick isolation when applying an external magnetic field, they have emerged as useful tools for the development of magnetic solid-phase extraction (m-SPE) protocols that avoid centrifugation and separation steps, as previously mentioned.

Moreover, these magnetic nanoparticles (MNPs) are often modified to give composite materials with a magnetic core and a functional shell that can provide more active sites for adsorption, while protecting the magnetic core. These composite materials are most commonly used for the extraction of plant samples. For instance, cellulose MNPs have been developed for the extraction and determination of polychlorobiphenyls (PCB) in juice samples [93] and magnetic β-cyclodextrin (CD) modified graphene oxide nanoparticles (Fe_3O_4@SiO_2/GO/β-CD) have been applied as a sorbent for m-SPE of plant growth regulators from vegetable methanolic extracts [94,95]. MNPs that were functionalized with tetraethyl orthosilicate, 3-(trimethoxysilyl)propyl methacrylate, polymethacrylate and combinations of the three have very recently been successfully adopted for the determination of brominated flame retardants in red fruit samples (strawberries, blueberries, and raspberries) using GC-MS and QuEChERS extraction. The MNPs were used for the clean-up of the extracts, and proved to have excellent adsorption ability for pigment matrices and other co-extracts, and to be very easy to recover simply using an external magnet [96].

Very interestingly, MNPs that were coated with an amino-terminated supramolecular cucurbit-[6]-uril pseudorotaxane motif have been developed for the extraction of polar compounds and, in particular, salvianolic acids. The investigated MNPs showed improved adsorption capacity towards the target analytes, compared to the non-functionalized NPs, while the combination of electrostatic interactions, van der

Waals interactions, hydrophilic interactions and hydrogen bonding was thought to be the driving force behind the interaction between the analytes and sorbent. In addition, the developed MNPs provided good recyclability and stability. These qualities were exploited when the sorbent material was successfully adopted for the determination of four salvianolic acids from *Salvia miltiorrhiza* Bunge root water extracts, showing excellent recovery and quantification performance [97].

Most of the magnetic composite nanoparticles applied in the plant field are composed by magnetic nanoparticles coated with metal organic frameworks (MOFs) that are used because of their large surface areas, high porosity, uniform pore sizes and structural diversity. These composite sorbents will be thoroughly described in the following section.

3.4 Reticular materials

Reticular materials are another important group of novel solid sorbents. They are large crystalline frameworks made up of building blocks linked by either covalent or coordination bonds, depending on the type of reticular material. These materials are characterized by impressive porosity, good chemical and thermal stability, and by the possibility of post-synthetic modification, which makes them suitable sorbents for microextractions. The large variety in building blocks means that it is possible to prepare innumerable reticular materials with different selectivities. The most common types of reticular materials are metal-organic frameworks (MOFs) and covalent-organic frameworks (COFs), which are mainly differentiated by the organic or inorganic nature of their building blocks. COFs only include organic molecules with non-metallic light elements (C, H, O, N, B and Si), which are then linked by covalent bonds that are ordered in two- or three-dimensional networks, while MOFs are made up of metal ions or metallic clusters and organic linkers as building blocks, connected by strong coordination bonds

[98]. Of the two classes of reticular materials, MOFs have been more widely applied in the plant field.

Mainly used for the extraction of contaminants from plant extracts [99,100], MOFs have also shown great potential as sorbents in combination with microextraction methods to extract active compounds from plants and plant products. However, their applications in this field are still quite limited as only a few studies on this possible use can be found. For example, a copper-based MOF has been adopted for the selective isolation of chamazulene, a compound with antiphlogistic effects, from a chamomile hexane extract. The driving force behind this selectivity is probably the chemical structure of the target compound, which is different from the other components in the extract, as chamazulene is the only aromatic compound [101]. A zeolitic imidazolate framework has also been investigated for use as a model MOF for the selective extraction of 3,4-dihydroxy-8,9-methylenepterocarpan (an antioxidant flavonoid derivative) from an *Caragana jubata* (Pall.) Poir ethanolic extract. In this case, an adsorption mechanism study has shown that the target compound is adsorbed onto the MOF surface, and that the *o*-phenolic hydroxyl group plays a significant role in the selective adsorption of the investigated flavonoid [102].

As can be seen in the above-cited examples, one of the main advantages of the use of MOFs in solid-phase extractions is the ability to selectively extract specific analytes and increase their enrichment. However, it should be noted that the raw plant material has to be submitted to analyte pre-extraction. This step is usually carried out with organic solvents, thus decreasing the sustainability of the extraction method. In addition, a back-extraction with another solvent (usually in low amounts) is necessary to release the target analytes from the MOF for downstream analytical determinations. In fact, attention must be paid to the fact that analytes are strongly adsorbed by MOFs, meaning that their desorption must be carefully optimized.

MOFs can be used in MSPD extractions as a very interesting alternative that can avoid analyte pre-extraction. As previously mentioned, MSPD has the significant advantages of lower organic-solvent consumption and cost, and of showing, at the same time, high extraction efficiency and selectivity. Furthermore, the subsequent purification procedure is very simple and short. MSPD can be used for the extraction and clean-up of solid, semi-solid and highly viscous samples, thus making it suitable for extractions from plant matrices. It is followed by the elution of the extracted analytes with a small amount of a suitable solvent. For instance, a zirconium-based MOF (MOF-808) has been applied for the MSPD extraction of ginsenosides from *Panax ginseng* C.A. Meyer. In detail, the ginseng leaves were directly ground with MOF-808 and the mixture was packed between two Teflon frits in a glass cartridge. Only two hundred microliters of methanol were used for the elution and the collected filtrate was analyzed using UHPLC-ToF-MS. This protocol gave higher extraction efficiency, simpler operation, a cleaner extract and lower organic-reagent consumption than a traditional extraction [103].

Besides the use of MOFs alone, the current trend is their combination with other materials to obtain (nano)composites. As previously mentioned, MOFs are very commonly combined with magnetic nanoparticles to increase the magnetic susceptibility. The combination of magnetic Fe_2O_4 nanoparticles with a zinc-based metal organic framework (MOF-5) has been successfully applied for the extraction of colchicine, a bioactive alkaloid, from autumn and spring *Colchicium* spp. root ethanolic extracts. Extraction was combined with ultrasound sonication that provided an incremental mass transfer and the sorbent was easily separated from the sample matrix by an external magnetic field. Colchicine sorption occurs by combination of various mechanisms such as ion exchange, hydrogen bonding, electrostatic, π-π, and dipole-ion interaction. In particular, ionic bonding between the negatively charged functional groups of colchicine and the positively charged centers of both Zn^{2+} in MOF and Fe^{3+} in Fe_2O_4 may be the main reason behind the fast and high colchicine adsorption on this hybrid phase [104]. $SiO_2@Fe_3O_4$ magnetic nanoparticles have been anchored onto an aluminum-based MOF (MIL53) and used for the extraction of aflatoxin B1 from several herbal teas via magnetic SPE coupled with spectrofluorimetric determination (see figure 2c) [105]. Furthermore, $SiO_2@Fe_3O_4$ magnetic nanoparticles have also been grafted onto a titanium-based MOF for the extraction of caffeic acid from methanolic/water extracts and coupled to HPLC-UV analysis [106]. Magnetic metal-organic-framework nanoparticles can also be adopted to speed-up the mechanochemical extraction (MCE) of analytes from plant samples. MCE is a room-temperature process that disrupts biomolecular lipid layers and cell walls using a multi-directional, mechanical in-liquid collision between the sample and specialized ceramic beads to achieve the complete release of target compounds, while preserving their chemical integrity, into the surrounding solvents. This technique can be combined with m-SPE with $Fe_3O_4@MOF$, meaning that the extraction of the analytes and their enrichment can be performed in one single step with the very fast removal of the extraction phase using a simple magnet. This approach has been successfully applied in the determination of organochlorine pesticides in tea leaves, but also shows great potential for other applications in the plant field [107].

Combining MOF with silica nanoparticles is another interesting possibility. As an example, a chromium-based MOF (MIL-101), combined with polyaniline (PANI), which was used as a conducting polymer, has been doped with silica nanoparticles and used for the efficient solid-phase extraction of thymol and carvacrol from *Mentha longifolia* (L.) L. plant extracts and a honey sample [108].

In addition, MOFs can be coated onto different carrier substrates. For instance, a zirconium-based MOF has been coated onto cotton fibers thanks to modifications to the cellulosic surface of the cotton substrate with carboxyl groups, which serve as active sites for the growing Zr-MOF. The sorbent, packed into a pipette tip, has been successfully used for the extraction of phenoxy herbicides from cucumber-water extracts [109]. MOFs have also been coated onto polymeric monolithic columns and adopted for the on-line SPE and determination of ursolic acid from several ethanolic plant extracts [110,111] and of aristolochic acid from methanolic plant extracts [112].

MOFs have also recently been grafted onto SPME fibers [113], as a means to couple the simplicity and performance of the technique with the previously mentioned outstanding properties of these materials. However, their use in the plant field has not yet been widely explored, but future applications are expected.

3.5. Carbon-based materials

Carbon-based materials also present exceptional physical and chemical properties, such as versatility, large surface areas with delocalized π-electrons, and easily modifiable surfaces. They constitute a group of different hexagonal structures of sp^2 hybridized carbon atoms. A single layer of these materials is called graphene. This carbon allotrope, together with graphene oxide (GO), and reduced graphene oxide (rGO), are the most representative two-dimensional forms. The difference between them lies in the presence of oxygen functional groups on their surface and their water solubility, with graphene and rGO that are non-polar and hydrophobic materials with high affinity towards carbon ring structures, while GO is hydrophilic. The three-dimensional forms of graphene are single or multiple wall carbon nanotubes (CNTs). CNTs share the same exceptional properties as graphene and its derivatives, but with a few differences as the inner walls of these materials are blocked by steric hindrance [114].

Both two and three-dimensional carbon-based materials have been applied in the plant field although graphene and GO are rarely used alone because they are prone to form aggregates. Ionic liquids can be adopted to prevent the aggregation of graphene, increasing, at the same time, the ability of π-π interactions, ionic exchange, electrostatic interactions and hydrogen bonding between the sorbent and the analytes. An IL-functionalized graphene adsorbent has, in fact, been developed for the pipette-tip solid-phase extraction of auxins from soybean sprouts [115].

However, graphene and, even more, GO are mainly applied to modify other sorbent materials to form composites [69,116,117]. For instance, GO has been added to a composite made of sporopollenin (see paragraph 3.1) and Fe_3O_4 MNPs to increase the adsorption capacity and selectivity towards polar compound of the sorbent material. The composite has been then adopted to the determination of polar organophosphorus pesticides in several vegetables that had been pre-treated with water and methanol [116].

Due to their high hydrophobicity, MWCNTs can be successfully applied for the clean-up of plant extract. In fact, they can provide very high chlorophyll removal and a decrease in the matrix effect, therefore making them very useful in HPLC analyses, in particular when coupled to mass spectrometry [118]. For instance, MWCNTs have been successfully applied to remove interferences from vegetables submitted to the QuEChERS procedure for the determination of exogenous compounds as paraben residues. MWCNTs provided up to a 94% reduction in chlorophyll and lower matrix effects compared to the commonly used primary-secondary amine (PSA) sorbent thus making the extracts fully compatible with HPLC–MS/MS analyses [119].

MWCNTs can also be combined with other adsorbent materials to form MWCNT composites that have become promising sorbent materials for SPE in recent years. In particular, combinations with magnetic nanoparticles increase the number of nanotube active sites, and provide excellent adsorption capacity. Fe_3O_4/MWCNT composites have been used as SPE sorbents for simultaneous determination by UHPLC-MS/MS of zearalenone and other mycotoxins in the acetonitrile/water extracts of *Salvia miltiorrhiza* Bunge roots and ryzhome [120] and for the extraction of a set of 11 chiral pesticides from several plant extracts [121]. MWCNTs can also be grafted with β-cyclodextrins. In this case, the cyclodextrins increase the absorption capacity of the composite thanks to their ability to form host–guest inclusion complexes with the target compounds in the inner cavities of their cone-shaped structures. For instance, multiwalled carbon nanotube-β-cyclodextrin composites have been incorporated into a poly(butyl methacrylate-ethylene dimethacrylate) monolith for the online extraction of psoralen and isopsoralen from a methanolic *Cullen corylifolium* (L.) Medik. (syn. *Psoralea corylifolia* L.) fruit extract [122].

MWCNTs composites incorporated in SPME fibers show a great potential also for *in-vivo* analyses. A very interesting application has been reported in a study in which a multiwalled carbon nanotubes/polyaniline-polypyrrole@polydimethylsiloxane (MWCNTs/PANI-PPy@PDMS) fiber has been prepared by electrodeposition strategy followed by polymer surface modification. The fiber was then used for the *in-vivo* extraction of pesticides from garlic by direct contact SPME, as represented in figure 2a [123].

4. Concluding remarks

Although new extraction phases are rarely originally developed for the extraction of plants and plant products, these samples can represent a good assessment for the efficiency of the new materials because of the complexity of natural matrices and the chemical variety of natural compounds.

Most of the studies that deal with the analytical characterization of natural products, in particular for metabolomics purposes, still adopt traditional extraction techniques and solvents. However, it is possible to note, from a literature survey, that there is a wide range of new phases that can cover all the range of topics dealing with plant analysis and increasing, at the same time, the sustainability and the selectivity of the extraction process.

New liquid phases, such as ionic liquids and deep eutectic solvents, can be directly used for the extraction of analytes from solid plant materials. These green solvents are significantly more sustainable than organic solvents at a microscale level and, at the same time, have the tremendous advantage that they can be tailored to the extraction of the classes and compounds of interest, thus decreasing the number of interfering components. In this respect, deep eutectic solvents and, in particular, natural deep eutectic solvents have found a huge number of applications in the extraction of natural samples and have the potential to replace traditional solvents, at least partly.

Furthermore, new solid sorbents also show great potential in the plant field. They can be used for the clean-up of complex samples as well as to increase enrichment and selectivity towards specific compounds. In this respect, the use of natural sorbents is a more sustainable approach for natural-product extraction, and it is expected that new biocompatible and efficient sorbents will be developed in the near future. The use of molecular imprinted polymers is still the most common approach to increase the extraction selectivity. Although this method cannot be considered “new”, the current trend is to combine these compounds with other extraction phases to produce composites that improve extraction efficiency and selectivity. In general, the merging of different classes of sorbents to produce hybrid materials is the current trend in analytical sample preparation, and the development of new hybrid phases has just started. These hybrid phases merit thorough investigation in the future, in particular for plant applications.

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Artwork

Figure 1. Overview of the main extraction phases employed as sorbent in liquid and solid phase extraction in plant field (A) and scheme of the structural characteristics of the main extraction phases employed in plant field (B).

Figure 2. Representative examples of extraction procedures using innovative sorbents in plant field: A) in-vivo SPME using a MWCNTs-based SPME fiber, adapted from Ref. [123], with permission from Elsevier; B) switchable temperature-responsive ionic liquid-based method for the simultaneous extraction and *in-situ* separation of lipophilic and hydrophilic compounds, adapted from Ref. [30], with permission from The Royal Society of Chemistry; C) m-SPE using a MOF-NPs hybrid material, adapted from Ref. [105], with permission from Wiley D) potentiometric analysis using MIP-based electrochemical sensor, adapted from Ref. [85], with permission from Institute of Food Technologists; and E) MSPD microextraction using microcrystalline cellulose as sorbent, adapted from Ref. [62], with permission from Elsevier.

Tables

Table 1. Main features of innovative extraction phases in plant field.

Feature	**ILs**	**DESs**	**Natural sorbents**	**MIPs**	**MNPs**	**Reticular materials**	**Carbon materials**
Pre-treatment of the sample	+/-	-	+/- (MSPD[a])	+	+	+/- (MSPD[a])	+
Extraction time (min)	10-30	30-120	1-5	+/-[b]	+/-[b]	+/-[b]	+/-[b]
Solvent consumption	-	-	+	+	+	+	+
Hybrid phases	+ [25]	+ [45]	+ [75]	+ [87]	+ [117]	+ [107]	+ [116]
Example of automatation	-	-	-	+ [83]	-	-	+ [122]
Microextraction	+ [32, 18]	-[c]	+ [67]	+ [86]	+ [96]	+ [104]	+ [123]
Re-use	+ [18]	+ [42]	+ [69]	+ [83]	+ [97]	+ [102]	+ [117]
Commercially available	+	+	+/-	+	+	+	+

+/- depend on the application/technique

[a] matrix solid-phase dispersion

[b] from few seconds to more than 30 minutes

[c] possible, but no applications found in plant field

Table 2. Representative applications of innovative extraction phases in plant field.

Sample	**Analytes**	**Phase**	**Additional materials**	**Extraction method**[a]	**Analytical platform**	**Ref.**
IL-based extraction						
Camellia sinensis (L.) Kuntze	polyphenols	multi-tentacled $PVAIm^+Pro^-$ $@SiO_2$[b]	silica	dSPE	HPLC-MS/MS	[24]
Elaeagnus rhamnoides (L.) A.Nelson	essential oil, non-volatile compounds	$[C_4mIm]^+[Br]^-$[c]	/	UA/MA distillation extraction	HPLC-UV/GC-MS	[26]
Coptis spp.	berberine hydrochloride	MIL two phase system $[N_{1\ 1\ 5\ 2OH}]^+[Br]^-$ and $[TEMPO\text{-}OSO_3]^-$ $[Na]^+$[d]	/	magnetic ABS	HPLC-UV	[18]
Chrysanthemum spp.	lipophilic and hydrophilic endogenous compounds	Temperature-responsive $[HMIM]^+[BF_4]^-$[e]	/	*in-situ* solid-liquid extraction	UHPLC-UV-QTOF-MS	[30]
DES-based extraction						
Trachycarpus fortunei (Hook.) H.Wendl.	polyphenols	ChCl/Ph[f] sorbent ChCl DES eluent	/	SPE	HPLC-MS	[42]
Mentha×piperita L.	volatile monoterpenes, phenols	ChCl/D(+)-glucose	/	solid-liquid UAE	UHPLC-QTOF-MS/GC-MS	[55]
Rosmarinus officinalis L.	phenols	ChCl/1,2-Propanediol	/	solid-liquid UAE	HPLC-UV	[57]
Taxus wallichiana var. *chinensis* (Pilg.) Florin	taxanes	menthol/1-propanol	/	solid-liquid UAE	HPLC-UV	[47]
Natural sorbent-based extraction						
Eriobotrya japonica (Thunb.) Lindl.	triterpenoid acid	MCC[g]	/	MSPD	UHPLC-QTOF-MS	[62]
Fruits	triazole fungicides	carbon (from pomelo peel) NPs	Fe_3O_4	m-SPE	GC-MS	[74]
Azolla imbricata (Roxb. ex Griff.) Nakai	caffeoylquinic acid derivatives	chitosan	/	MSPD	HPLC-UV	[64]
MIP-based extraction						

Phyllanthus urinaria L.	corilagin	Corilagin-MIP	$[BMIM]^+[BF_4]^-$[h]	SPE	HPLC-UV	[87]
Tussilago farfara L.	pyrrolizidine alkaloids	PA[i]-MIP	/	SPME	UHPLC	[86]
Edible plant	gallic acid	GA[l]-MIP	/	/	IES[e] potentiometric analysis	[85]
MNP-based extraction						
Salvia miltiorrhiza Bunge	salvianolic acids	magnetite@silica NPs	curcubit pseudorotaxane complex	m-dSPE	HPLC-MS	[97]
Reticular material-based extraction						
Panax ginseng C.A.Mey	saponins	MOF-808	/	μ-MSPD	UHPLC-QTOF-MS	[103]
Camellia sinensis (L.) Kuntze	organochlorine pesticides	MIL-100	Fe_3O_4	m-SPE	UHPLC-UV/GC-MS	[107]
Carbon material-based extraction						
Vegetables	parabens	MWCNTs	/	QuEChERS (SPE)	HPLC-MS/MS	[119]
Allium sativum L.	pesticides	MWCNTs	PANI-PPy@PDMS[m]	DI/*in-vivo*/*in-vitro* SPME	GC-MS	[123]

[a] for the acronyms of the techniques, see abbreviation list

[b] silica particles with polyvinyl alcohol chains modified by N-methyl imidazole proline salt

[c] 1-butyl-3-methyl imidazole bromine salt

[d] alkyl-(2-hydroxyethyl)-dimethylammonium bromides, sodium 4-sulfonatooxy-2,2,6,6-tetramethyl piperidine-1-yloxyl

[e] 1-hexyl-3-methylimidazolium tetrafluoroborate

[f] phenol

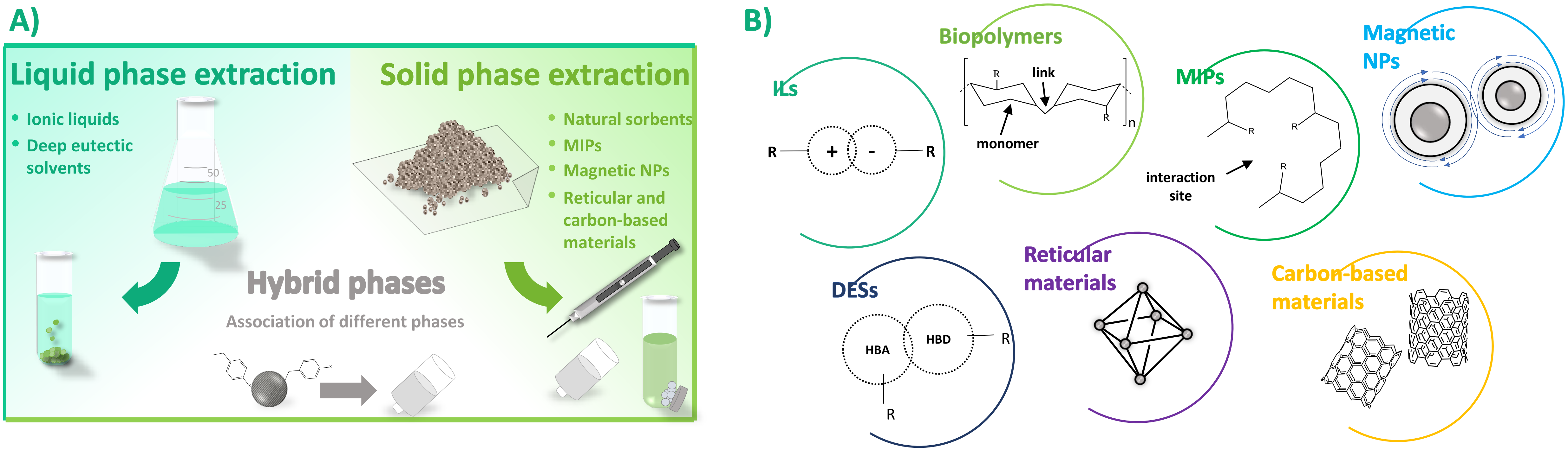
[g] microcrystalline cellulose

[h] 1-butyl-3-methylimidazolium tetrafluoroborate

[i] pyrrolizidine alkaloid

[l] gallic acid

[m] polyaniline-polypyrrole@polydimethylsiloxane


A)
Liquid phase extraction
Ionic liquids
Deep eutectic solvents
50
25
Solid phase extraction
Natural sorbents
MIPs
Magnetic NPs
Reticular and carbon-based materials
Hybrid phases
Association of different phases
B)
ILs
R
+
-
R
Biopolymers
R
link
R
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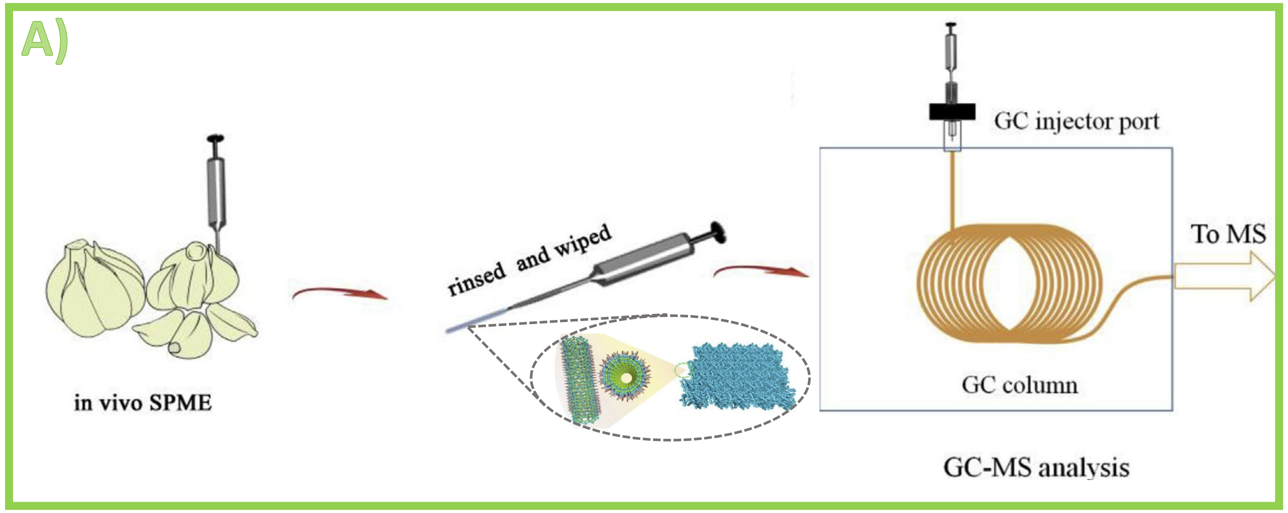
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To MS
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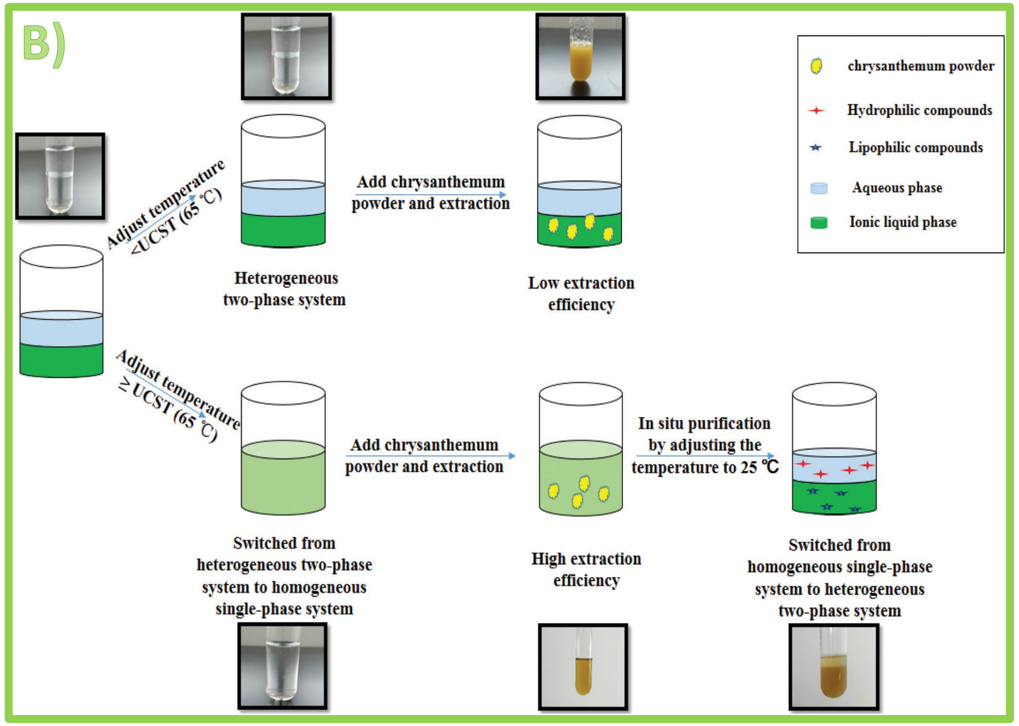
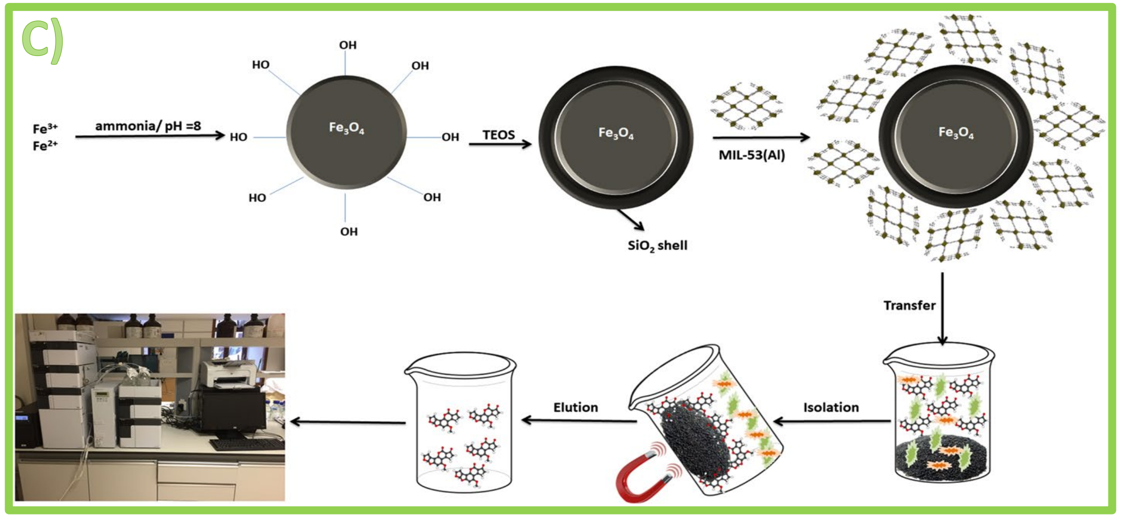
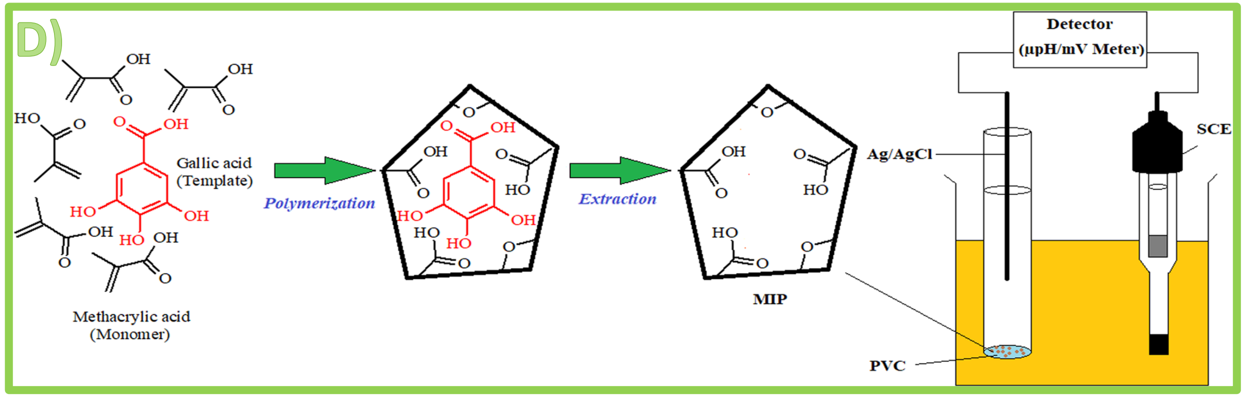
GC-MS analysis


B)
chrysanthemum powder
Hydrophilic compounds
Lipophilic compounds
Aqueous phase
Ionic liquid phase
Adjust temperature <UCST (65 ℃)
Heterogeneous two-phase system
Add chrysanthemum powder and extraction
Low extraction efficiency
Adjust temperature ≥ UCST (65 ℃)
Switched from heterogeneous two-phase system to homogeneous single-phase system
Add chrysanthemum powder and extraction
High extraction efficiency
In situ purification by adjusting the temperature to 25 ℃
Switched from homogeneous single-phase system to heterogeneous two-phase system


C)
Fe³⁺
Fe²⁺
ammonia/ pH =8
HO
OH
Fe₃O₄
TEOS
SiO₂ shell
MIL-53(Al)
Transfer
Isolation
Elution


D)
OH
HO
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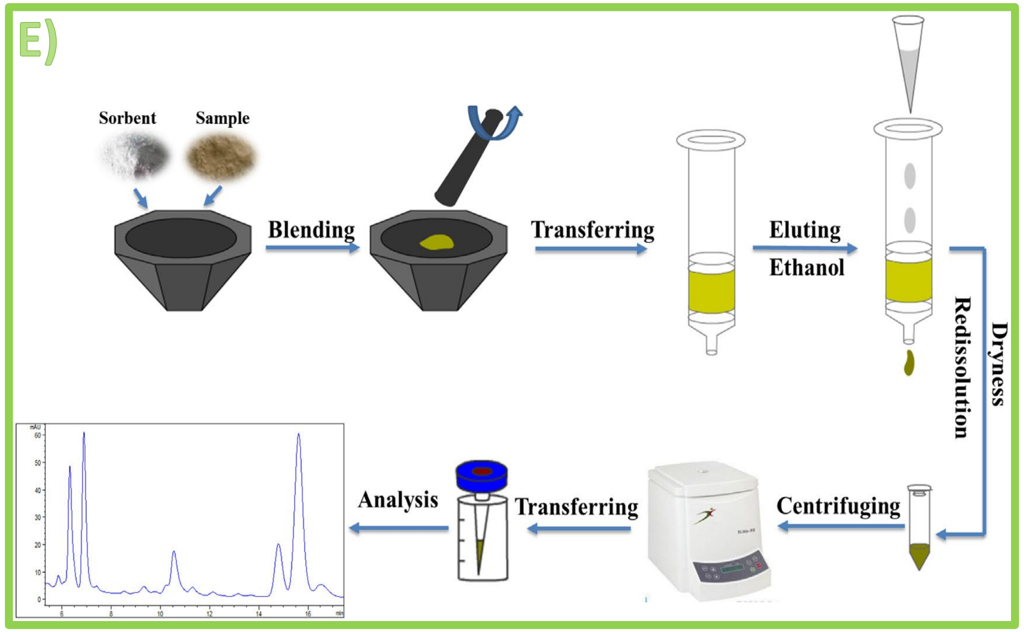
Gallic acid (Template)
Methacrylic acid (Monomer)
Polymerization
Extraction
MIP
Detector (μpH/mV Meter)
Ag/AgCl
SCE
PVC


E)
Sorbent
Sample
Blending
Transferring
Eluting
Ethanol
Dryness
Redissolution
Centrifuging
Transferring
Analysis