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REVIEW

Microextraction of bioactive compounds using deep eutectic solvents: a review

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Abstract

Analytical scientists are actually developing sustainable methods for the analysis of environmental samples. In particular, replacing classical, toxic solvents by safer solvents is a principle of green chemistry. For instance, deep eutectic solvents, formed by mixing two or more components by hydrogen bonding, appear promising. Here, we review the use of deep eutectic solvents for liquid–liquid, liquid–solid and combined extractions. We compare the use of deep eutectic solvents with conventional organic solvents for extraction. Overall, deep eutectic solvents showed better extraction efficiency and higher recovery compared to water and conventional organic solvents. In particular, deep eutectic solvents showed about 93–99% efficiency for protein extraction. The extraction efficiency often depends on the physicochemical properties of deep eutectic solvents.

Keywords Bioactive compounds · Combined extraction techniques · Deep eutectic solvents · Green chemistry · Liquid–liquid-phase microextraction · Physicochemical properties · Proteins · Solid-phase microextraction

Abbreviations

DES	Deep eutectic solvent
DI-SDME	Direct immersion single-drop microextraction technique
HS-SDME	Headspace single-drop microextraction technique
TDES-MIP	Ternary deep eutectic solvent molecularly imprinted polymer

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Introduction

In the past decades, pharmaceutical industries revived the interest of plant-derived natural products in drug discovery (de Cássia da Silveira e Sá et al. 2014). In addition to their pharmaceutical applications, natural bioactive molecules are also used in the production of agrochemicals, nutraceuticals, cosmetics, etc. (Azmir et al. 2013). On another note, extraction and purification of proteins has become very interesting for biotechnology industry and for research and pharmaceutical applications (Huang et al. 2015). Extracting these valuable compounds from their original matrix into an adequate solvent is very challenging because the extraction method should follow the principles of the green chemistry while being time-saving, cheap and revealing a high yield (Rezaee et al. 2006; Anastas and Eghbali, 2010).

Conventional separation techniques, such as liquid–liquid extraction, solid-phase extraction, coprecipitation, as well as many exhaustive extraction methods (maceration, steam or hydro-distillation, pressing, decoction, infusion, percolation and Soxhlet extraction), were long considered for extraction-related applications before being described as expensive, labor-intensive and time-consuming techniques (Chemat et al. 2012). Consequently, new extraction methodologies have arisen such as solid-phase microextraction and liquid-phase microextraction (Hawthorne et al. 1992; Pedersen-Bjergaard and Rasmussen, 1999). These techniques

are characterized by using low amounts of sample matrices and small volumes of organic solvents. They are recently recommended because they offer many advantages such as increased concentration and minimized extraction time and energy consumption (Aydin et al. 2018). However, using toxic organic solvents in these extraction techniques is still a controversial subject (Mohebbi et al. 2018).

Deep eutectic solvents were first described by Abbott et al. in the early 2000's (Abbott et al. 2003). These solvents are prepared by mixing two or more components that can form hydrogen bonds (Moura et al. 2017). Due to different interactions (Van der Waals and hydrogen bonds), these solvents have much lower melting point than that of their individual components (Abbott et al. 2004). Natural deep eutectic solvents are formed by natural metabolites produced from cells such as urea, alcohols, organic acids, amines, amino acids, sugars and choline (Vanda et al. 2018). Deep eutectic solvents and natural deep eutectic solvents are characterized by a low vapor pressure, nonflammability, a high thermal stability and a low thermal conductivity (Nam et al. 2015; Radošević et al. 2016; Khataei et al. 2018). The first hydrophobic deep eutectic solvents were synthesized from decanoic acid and quaternary ammonium salts and used for the extraction of volatile fatty acids from aqueous solutions (van Osch et al. 2015). Deep eutectic solvents are considered "green," and excellent alternatives to conventional and nonconventional organic solvents, being effective to extract hydrophilic and hydrophobic compounds (Tang et al. 2014).

This review presents an emphasis on the microextraction techniques that used deep eutectic solvents as extraction solvents. Also, the effects of these solvents properties on the extraction efficiency are discussed. In addition, this review examines the advantages and drawbacks of each extraction method, used alone or in combination with a second extraction technique. A brief variation of a single method parameter (such as temperature and extraction time) can affect the extraction efficiency. However, given the large number of parameters as well as the microextraction techniques, little information regarding the method parameters is described in this review. A more comprehensive and extensive bibliography can be found in the corresponding book chapter. This review is an abridged version of the book chapter by Nakhle et al. (2021).

Microextraction techniques

Liquid-phase microextraction

Different liquid-phase microextraction techniques exist such as single-drop microextraction, hollow-fiber liquid-phase microextraction and dispersive liquid–liquid microextraction.

Single-drop microextraction

Headspace single-drop microextraction (Fig. 1) is applied for the extraction of volatile or semi-volatile compounds from a complex matrix because the suspended solvent drop is exposed only to the headspace of the sample. Tang et al. (2014) applied this method to extract terpenoids using the optimal deep eutectic solvent choline chloride/ethylene glycol (1:4 molar ratio), which showed the best extraction efficiency. A pronounced advantage was observed compared to other conventional methods (ultrasonication and heat reflux extraction) using methanol as extraction solvent (Tang et al. 2014). Also, Yousefi et al. (2018) validated the efficacy of this method in the extraction of aromatic hydrocarbons using a hydrophobic deep eutectic solvent-magnetic bucky gel. The solvent drop was formed by mixing the optimal deep eutectic solvent (choline chloride/chlorophenol 1:2 molar ratio) with magnetic multiwalled carbon nanotubes. This mixture made the solvent drop more stable. It was then demonstrated that heating and increasing the stirring rate decreased the extraction time (Yousefi et al. 2018).

Direct immersion single-drop microextraction (Fig. 1) is applied for the extraction of nonvolatile compounds and polar analytes. Gu et al. (2014) used this method for the extraction of phenolic compounds (phenol, *p*-cresol and

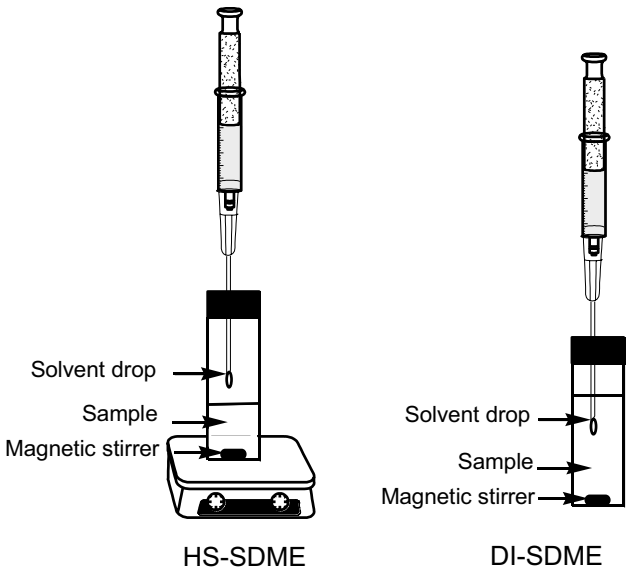

Fig. 1 Headspace single-drop microextraction technique (HS-SDME) and direct immersion single-drop microextraction technique (DI-SDME). In HS-SDME, the solvent drop is exposed to the headspace of the sample and is not in direct contact with the matrix. The solvent drop adsorbs the target compounds volatilized from the sample matrix heated and stirred for a specific time. In DI-SDME, the solvent drop is immersed directly in the sample phase. Herein, the acceptor solvent should be immiscible with the donor phase as the solvent drop is immersed in it. After extraction, the solvent drop is retracted back into the microsyringe and analyzed

β-naphtol) from crude oils with 10 µL of choline chloride/ethylene glycol (1:3 molar ratio) deep eutectic solvent. Ultrasonication was also applied for obtaining a better yield because polar compounds are being extracted from nonpolar solutions. According to authors, this solvent exhibited a better extraction efficiency than water or than the solutions of the individual components of the deep eutectic solvent (Gu et al. 2014).

Hollow-fiber liquid-phase microextraction

This microextraction method can be used for the extraction of components from complicated biological fluids. Interestingly, this technique prevented the diffusion of large molecules from the donor phase to the acceptor phase (Khataei et al. 2018), as a consequence of the use of a porous polypropylene hollow-fiber membrane (Fig. 2).

This method was used by Khataei et al. (2018) for the extraction of steroidal hormones (dydrogesterone and cyproterone acetate) from urine and plasma samples using methyltriphenylphosphonium iodide ($Me(Ph)_3PI$)/ethylene glycol (1:4 molar ratio) plus 20% v/w methanol. Compared to other extraction techniques defined later on, such as hybrid solid-phase extraction, solid-phase extraction, hollow-fiber liquid–liquid microextraction, this technique has the lowest limit of detection and a wider linear range in both plasma and urine matrices. In addition, clear chromatograms were obtained via this method (Khataei et al. 2018).

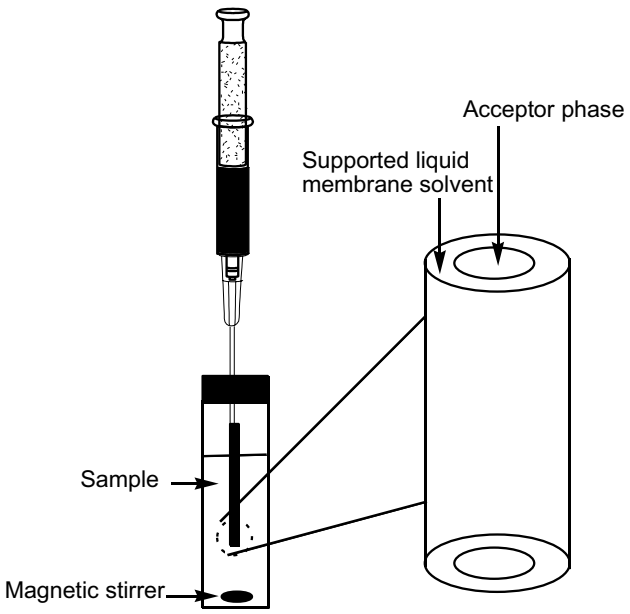

Fig. 2 Hollow-fiber liquid-phase microextraction technique. Three phases are present: the first one is the biological sample or the donor phase containing the target analytes; this phase is stirred in a sample vial. The acceptor phase is the second phase located in the lumen of the membrane. The third phase separates the two other phases: a supported liquid membrane solvent (immiscible with the two other phases) designated as the extraction phase; it is located inside the pores of the fiber membrane

Dispersive liquid–liquid microextraction methods

Such techniques are based on the formation of small droplets of extraction solvent which are dispersed throughout the aqueous phase. In this way, the contact surface between both immiscible phases is increased (Fig. 3) (Ribeiro et al. 2015).

When extracting benzoylureas, the binary solvents-dispersive liquid–liquid microextraction method was tested using low hydrophilic deep eutectic solvent as extraction solvent (Zeng et al., 2017). Exceptionally, there was no need for a dispersive solvent and this method presented the advantage of lower minimum detection value and higher enrichment factor than various other techniques (Zeng et al. 2017). Also, the linear ranges of the air-assisted dispersive liquid-phase microextraction method, when extracting nine pesticides using deep eutectic solvent, were equivalent or wider than other extraction methods. Higher extraction efficiencies were also observed (Farajzadeh et al. 2017). In addition, Moghadam et al. (2018) developed a similar microextraction procedure: air-agitated emulsification microextraction based on a low-density deep eutectic solvent for the extraction of antidepressant drugs from human plasma samples and pharmaceutical wastewater samples by three types of deep eutectic solvents. Compared to other conventional techniques, this method proved its ability for accurate analysis of trace levels of drugs close to the therapeutic/toxic ranges (Moghadam et al. 2018). For the extraction of rhodamine B, recoveries experiments showed a minimal efficacy of this method using the optimal deep eutectic solvent consisted of tetrabutyl ammonium chloride/decanoic acid (1:2 molar ratio) (97% extraction efficacy) compared to other extraction methods (Yilmaz and Soylak, 2018).

Deep eutectic solvent-based subcritical water extraction

Saravana et al. (2018a) proved that the extraction yield of polysaccharides obtained using the optimal deep eutectic solvent (70% water plus choline chloride/glycerol in 1:2 molar ratio) was at least twice of that obtained from a solution of HCl/water mixture, usually used to extract polysaccharides (Saravana et al. 2018a). Through adding 10–30% citric acid/alanine (1:1 molar ratio) deep eutectic solvent to water media, Machmudah et al. (2018) proved the efficacy of the resulting subcritical water extraction method to extract xanthones. Accordingly, scanning electron microscope images showed the disruption of the surface of the pericarps of mangosteen after treatment by this method at high temperature. The formation of pores was obviously observed via the pronounced cleavage

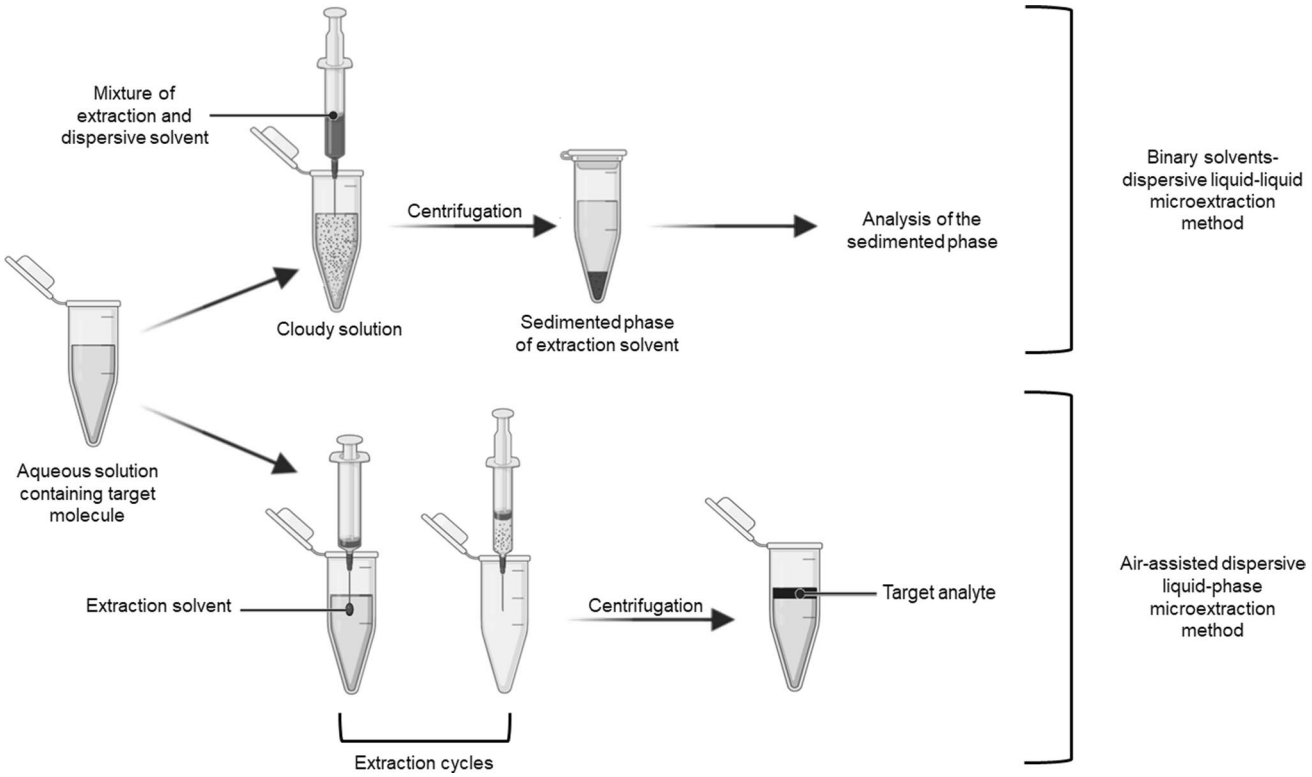

Fig. 3 Dispersive liquid–liquid microextraction techniques. In Binary solvents-dispersive liquid–liquid microextraction method, the dispersion of the solvent droplets is done by the help of a dispersive solvent that is miscible in both aqueous and extraction phases. The extraction solvent phase is analyzed after centrifugation. In the gas-associated dispersive liquid-phase microextraction, the dispersing solvent is replaced by a gas. With air as gas, the method is called air-assisted dispersive liquid-phase microextraction. This method consists on multiple sucking and injecting processes via a syringe. At this stage, the target analytes are extracted into the fine droplets of the extraction solvent. Figure created with BioRender.com

of intermolecular and intramolecular bonds in and/or between lignin, cellulose, and hemicellulose by deep eutectic solvent (Machmudah et al. 2018).

Deep eutectic solvent-based aqueous two-phase system

This technique is widely used to extract proteins from biological fluids, as it prevents their denaturation and preserves their biological activity (Du et al., 2007; Li et al., 2016; Xu et al., 2015; Zeng et al., 2014). The detailed process of the aqueous two-phase system is illustrated in Fig. 4.

The presence of relatively high salt concentration resulted in a competition between the salt ions and bovine serum albumin for water molecules. Due to the decrease in the amount of water required for the solubilization of the protein, the solubility of bovine serum albumin in the salt phase was tremendously decreased, resulting in the increase in its concentration in the deep eutectic solvent

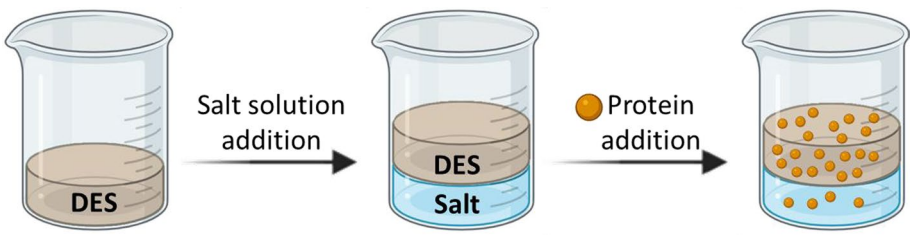

Fig. 4 Deep eutectic solvent (DES)-based aqueous two-phase system extraction method. Two aqueous phases are present in this technique: the DES-rich aqueous phase and the salt-rich aqueous phase. When these phases components are mixed above a certain salt critical concentration, they are separated into two unambiguous aqueous phases. It is then where the proteins present in the sample are partitioned between these two phases with a higher affinity for the DES-rich aqueous phase. Figure created with BioRender.com

phase. UV–visible, Fourier-transform infrared spectroscopy and circular dichroïsm experiments showed no interference between all deep eutectic solvents and bovine serum albumin and that the conformation of the protein was maintained during extraction. The extraction process is mainly due to the aggregation of protein molecules that are expected to be surrounded by deep eutectic solvent (Xu et al. 2015).

Li et al. (2016) used six betaine-based deep eutectic solvents differing by their hydrophilic property, viscosity and density for the extraction of bovine serum albumin, trypsin and ovalbumin proteins from calf blood sample. The extraction efficiency using the optimal deep eutectic solvent was higher than 99% as the bovine serum albumin band (66 kD), obtained by SDS-PAGE analysis, was present in the deep eutectic solvent-rich top phase but was not detectable in the bottom phase. This method was validated for accuracy, repeatability and environment stability (Li et al. 2016).

Compared to polypropylene glycol-based aqueous biphasic system, the extraction efficiency of three hydrophobic dyes was enhanced with tetrabutylammonium bromide/polypropylene glycol 400 (1:2 molar ratio) deep eutectic solvent. It was found that the more hydrophobic the pigment is, the more it is extracted in the deep eutectic solvent-rich phase (Zhang et al. 2018).

Ultrasound microextraction

This technique involves a low volume of deep eutectic solvent (< 500 µL) and a short time of extraction (< 15 min) (Khezeli et al. 2016; Mouratoglou et al. 2016). Similar or larger amounts of flavonoids were extracted from *Chamaecyparis obtusa* leaves using this method with deep eutectic solvent with relatively low cost, low vapor pressure and low toxicity compared to other extraction method (heating and stirring) using conventional organic solvents (Bi et al. 2013). Also, higher extraction yield of polysaccharides was obtained with optimized conditions, in comparison with hot water extraction and water-based ultrasound extraction (Zhang and Wang 2017). Bajkacz et al. (2017) used natural deep eutectic solvent-based ultrasound microextraction procedure that provided high accuracy, sensitivity and high extraction efficiency for the simultaneous analysis of four isoflavones. This method was faster and showed higher recoveries with lower relative standard deviation in comparison with the Soxhlet extraction and microwave extraction methods (Bajkacz and Adamek, 2017). In addition, the extraction yield of wine lees anthocyanins was improved in comparison with alternative methods (stirring, heating, or heating and stirring) and with the extraction using conventional solvents (water, methanol, ethanol, 70% methanol, 70% ethanol) (Jeong et al. 2017).

Microwave extraction

Microwave extraction is known for many advantages: homogeneous heating, high speed and high heat efficiency, which may produce a high extraction efficiency at a short extraction time (Cui et al. 2015; Wang et al. 2018). Comparing to other conventional techniques, microwave extraction is faster and allows the automation of the extraction, but it is more costly and demands cleanup steps (Chen et al. 2016). Higher extraction efficiency was observed using deep eutectic solvent than other conventional solvents. The maximum extraction yield of baicalin using deep eutectic solvent-based microwave extraction was slightly higher than the extraction by 70% ethanol (vol) -based hot reflux-assisted extraction and higher than the ultrasound extraction (Cvjetko Bubalo et al. 2016; Chanioti and Tzia, 2018).

Vortex extraction

The suspension, composed of the extractant phase and the donor phase, is subjected to mechanical vortex stirring, leading to the extraction of the analytes in a tiny droplets form. Subsequently, the suspension is centrifuged (González et al. 2018; Ojeda and Rojas, 2018).

This process was pursued by García et al. (2016) for the extraction of phenolic compounds. An increase in the extraction yield of oleacein and oleocanthal of 20–33% and approximately 68%, was proved by extraction with choline chloride/xylitol and choline chloride/1,2-propanediol deep eutectic solvents, respectively, compared to the conventional solvent (80% methanol/water (v/v)) (García et al. 2016). Wang et al. (2017) explored the potency of choline chloride/ethylene glycol deep eutectic solvent to extract and quantify rhodamine B present in Chili oil. Its recovery value using deep eutectic solvent was 75% higher than in control experiments using water (10% recovery). Compared to methanol, deep eutectic solvent showed high selectivity for rhodamine B; however, other dyes were extracted also with methanol (Wang et al. 2017). Cao et al. (2018) applied a vortex extraction method for the extraction of proanthocyanidin. Sixteen different deep eutectic solvents were tested, and it was concluded that organic acid-based deep eutectic solvents were better than alcohol-based ones and this was related to the higher polarity of the organic acid-based ones suitable for the extraction of the hydrophilic proanthocyanidin. Extraction yield with choline chloride/malonic acid deep eutectic solvent (1:2 molar ratio) with 55wt% of water (22.19 ± 0.71 mg/g solvent) was much higher than those with conventional organic solvents (70% methanol (7.87 ± 0.21 mg/g solvent), 70% ethanol (7.84 ± 0.10 mg/g solvent) and 70% acetone (13.26 ± 0.54 mg/g solvent)) (Cao et al. 2018).

Heating and stirring

Such method is based on the solubilization of the target analytes in the deep eutectic solvent under heating and stirring conditions that are optimized depending on the target compound (Das et al. 2016; Bağda et al. 2017).

Dai et al. (2016) used natural deep eutectic solvent to extract anthocyanins from purple and orange petals of *Catharanthus roseus*. This method was compared with ultrasound extraction and ultrasound extraction with heating. The best extraction yield was obtained by heating and stirring at 40 °C, and it was 35–55% greater than that obtained with sonication at 25 °C (Dai et al. 2016). Also, Peng et al. (2018) obtained an improved yield of extracted rutin using deep eutectic solvent and water (18.1%) compared with the methanol–water solution or ethanol–water solution (60% water). The yellow rutin powder was obtained with a yield of 62.7% with purity higher than 95% and an excellent antioxidant activity (Peng et al. 2018).

Solid-phase microextraction

Solid-phase microextraction is based on the partition of the analytes between a liquid solution (sample phase) and a viscous liquid (deep eutectic solvent) immobilized on a solid support (sorbent phase) via absorption/adsorption mechanism (Okenicová et al., 2016). This technique is considered better than liquid–liquid microextraction because it reduces and even eliminates the use of toxic and inflammable solvents, thus becoming more environmentally friendly (Picó et al., 2007; Ince et al., 2010). Some of the commercially available cartridges present some limitations such as single adsorption mechanism and low special selectivity, which limit their further application (Li et al. 2017). Hence, scientists are working on the development of new selective sorbents via the application of deep eutectic solvents to increase their selectivity and capacity (Gan et al. 2016).

Ball mill-assisted extraction method

Ball-mill extraction method can provide a special, optimized motion to disrupt cells through the multi-directional, simultaneous beating of specialized beads on the sample to achieve full release of the target molecules into the solvent (Wang et al. 2016). Comparing to other extraction methods (methanol-based ultrasound extraction and heat reflux extraction), the ball mill-assisted extraction method, developed by Wang et al. in (2016), was faster with higher extraction capacity of tanshinones and lower consumption of solvents. Also, in comparison with conventional solvents (n-hexane, ethanol, methanol, acetonitrile, acetone, and ethyl acetate), it was demonstrated that with deep eutectic solvents (six different choline chloride-based deep eutectic solvents) higher extraction efficiencies were obtained likely because of multiple interactions between deep eutectic solvent and the target molecules. Extracted compounds were quite stable in deep eutectic solvents (Wang et al. 2016).

Magnetic solid-phase extraction method

This method has the same principle as the classical solid-phase microextraction, but it is mainly related to the magnetic sorbents facilitating the extraction process by applying an external magnetic field (Oller-Ruiz et al. 2018). Furthermore, these sorbents do not necessary need to be packed into cartridge and can be recycled and reused; also the centrifugation and the filtration could be avoided (Xu et al. 2016a, b). Huang et al. (2015) synthesized magnetic graphene oxide impregnated with deep eutectic solvent; the latter showed increased water solubility and improved proteins extraction efficiency than graphene oxide alone (Huang et al. 2015). The same method was used by Xu et al. (2016a, b) to extract proteins, without modification of their conformation. Also, Xu et al. (2016b) introduced a new type of polymer-immobilized magnetic silica materials with high thermal stability, extraction and recycling capacity for the extraction of trypsin (Xu et al. 2016b). Four choline chloride-based deep eutectic solvents-magnetic graphene oxide sorbent gave the best extraction efficiencies compared to magnetic graphene oxide and Fe_3O_4–NH_2 sorbents. This was linked to the numerous oxygen-containing functional groups existing on the surface of graphene oxide in addition to the hydroxyl groups of deep eutectic solvents that strengthen the interactions between proteins and deep eutectic solvents. In addition, the extraction efficiency was the best at a certain pH where opposite charges between magnetic microspheres and proteins exist. Another parameter related to the extraction capacity was the molecular weight of the proteins: the smaller the protein, the easier was its extraction (Xu et al. 2016a, b).

Li et al. (2017) developed a C_8-amino-bifunctionalized ordered mesoporous organosilica sorbent for the extraction of triazine herbicides from watermelon samples. Deep eutectic solvent composed of choline chloride/ethylene glycol 1:2 molar ratio was used as the extraction solvent. This method demonstrated high recoveries and lower limits of detection and relative standard deviations values than other methods (pressurized liquid extraction, nonaqueous cavitation extraction, molecular-imprinted polymer-based solid-phase microextraction, cloud point extraction and matrix solid-phase dispersion). These sorbents present many advantages such as large surface area, regular and uniform pore size, hydrothermal stability, and the availability of two functional groups combining hydrophobic and hydrophilic characters (octyl chains and amino groups, respectively), which improved the adsorption selectivity (Li et al., 2017).

Mini-solid-phase microextraction or pipette-tip solid-phase extraction method

The needle of the syringe system is suitable to be used as a meticulous mini-solid-phase microextraction cartridge because of its special miniconical shape (Li and Row, 2018).

This technique was applied by Li and Row in (2018) for the extraction of 3,4-dihydroxybenzoic acid from *Ilex Chinensis Sims* leaves using molecular-imprinted polymers as shown in Fig. 5. Ternary deep eutectic solvent was used by mixing choline chloride, ethylene glycol and 3, 4-dihydroxybenzoic acid. Compared to deep eutectic solvent-modified non-imprinted polymers (without template), a molecular-imprinted polymer (without deep eutectic solvent) and non-imprinted polymer (without deep eutectic solvent and without template); ternary deep eutectic solvent molecularly imprinted polymer demonstrated the best extraction efficiency. This technique presents an additional advantage than the other solid-phase extraction techniques since lower amounts of sorbent mass were used (Li and Row, 2018).

Combined extraction techniques

Deep eutectic solvent-based negative-pressure cavitation-assisted extraction method combined with macroporous resin enrichment

In this method, millions of tiny vapor bubbles are formed in the liquid by the help of a machine that induces pressure (for example pumps, turbines and propellers). The deep eutectic solvent extraction solution flowed through the column packed with macroporous resins. Deep eutectic solvent showed better extractability than 80% ethanol solvent. Moreover, deep eutectic solvent negative-pressure cavitation-assisted extraction yields were higher than that of deep eutectic solvent-based ultrasound extraction method (Qi et al. 2015). This method, which is performed at room temperature, can be widely used for the thermolabile compounds. Additionally, the oxidation of these compounds is avoided as air is excluded in the extraction process (Liu et al. 2009).

Microwave extraction and solid-phase extraction

Wei et al. (2015) used the microwave extraction method for the extraction of four flavonoids from *Radix Scutellariae*. Among the thirteen tested natural deep eutectic solvents, the choline chloride/lactic acid (1:2 molar ratio) + 20% water (v/v) mixture was selected because it was the most suitable for the simultaneous extraction of these compounds. A solid-phase extraction method was also applied where the natural deep eutectic solvent extraction solution was flowed through the column packed with ME-2 macroporous resin for the separation of the flavonoids (baicalin, wogonoside, baicalein and wogonin) from the natural deep eutectic solvent, with high recovery yields (Wei et al. 2015).

Biological and deep eutectic solvent pretreatments

The combination of the biological treatment and deep eutectic solvent was tested by Dai et al. (2017) for the removal of lignin and hemicellulose from bamboo shoot shell waste in order to enhance the biomass conversion into fermentable sugars for the producing of biofuel.

In this study, bamboo shoot shell was subjected to biological treatment with Galactomyces sp. CCZU11-1 used

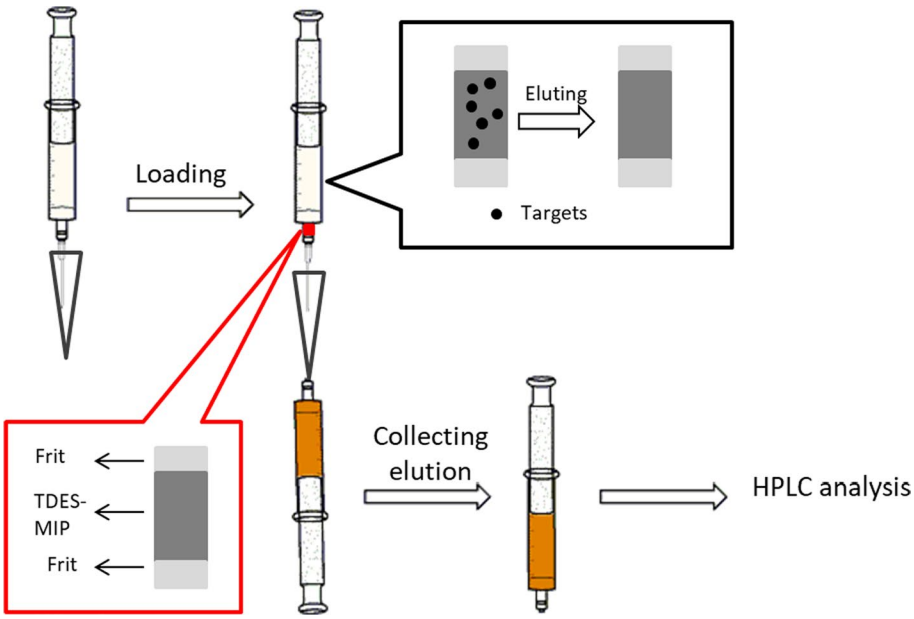

Fig. 5 Pipette-tip solid-phase extraction method. In this method, the sorbent is packed inside the end of the syringe (in this case, the sorbent is the ternary deep eutectic solvent molecularly imprinted polymer (TDES-MIP)). Each time the solution was sucked up into and out of micropipette type of the needle containing the adsorbent by pulling and pushing the syringe, respectively. The extraction complex retained on the adsorbent was washed, eluted and subjected to analysis

to produce cellulases. After fermentation, the residues of bamboo shoot shell were treated by deep eutectic solvent. Notably, choline chloride/oxalic acid (1:2 molar ratio) was found to be the best solvent for pretreating bamboo shoot shell with the highest xylan removal (53%) and delignification (48%). After deep eutectic solvent addition, more surface areas in the pretreated bamboo shoot shell were formed which allowed cellulases to further attack cellulose and residual hemicellulose. Thus, enzymatic saccharification of bamboo shoot shell was increased after deep eutectic solvent pretreatment. The reducing sugars yield from the enzymatic hydrolysis of 50 g/L deep eutectic solvent bamboo shoot shell was maximal (90%). Furthermore, it was found that the combination pretreatment was better than one step pretreatment and it effectively removed xylan and lignin after treatment with deep eutectic solvent (Dai et al. 2017).

Deep eutectic solvent-based vortex extraction combined with emulsification liquid–liquid microextraction

Aydin et al. (2018) developed a new technique using deep eutectic solvent (choline chloride/phenol 1:4 molar ratio) as a water-miscible extraction solvent for the extraction of curcumin. Recoveries of curcumin using different deep eutectic solvents were above 96% (Aydin et al. 2018).

Dispersive solid-phase extraction in combination with deep eutectic solvent-based air-assisted liquid–liquid microextraction

The process started with dispersive solid-phase extraction method. Then, air-assisted liquid–liquid microextraction method was applied. In the proposed method, the synthesized deep eutectic solvent was used as an elution/extraction solvent of tricyclic antidepressant drugs (amitriptyline, nortriptyline, desipramine, clomipramine and imipramine) from plasma and urine samples. Results showed many advantages such as good repeatability, high enrichment factors and extraction recoveries, low limits of detection and limits of quantification, and simplicity of operation. According to Mohebi et al. (2018), this method can be used for the routine analysis of many drugs in the pharmaceutical and clinical laboratories with no harm on human health and environment (Mohebbi et al. 2018).

Ultrasound extraction and solid-phase extraction

Liu et al. (2018) proposed a combined technique for the extraction of different classes of natural products (phenolics, terpenoids and phenolic acids) from *G. biloba* leaves and ginsenosides from *P. ginseng* leaves. Six different natural deep eutectic solvents were tested. The presence of natural deep eutectic solvent caused severe tailing of spots in high-performance thin-layer chromatography analysis; therefore, it was important to recover the analytes from natural deep eutectic solvent before analysis. Hence, solid-phase extraction method was employed using polymeric reversed-phase sorbent cartridges. Among the natural deep eutectic solvents, choline chloride/malic acid (1:1 molar ratio) and glycerol/proline/sucrose (1:1:1 molar ratio) were the best for *G. biloba* leaves, and choline chloride/malic acid (1:1 molar ratio) and glucose/malic acid (1:1 molar ratio) for *P. ginseng* leaves showing the highest yields of the target compounds. The addition of water to natural deep eutectic solvent affected the extraction and maximum yields. The latters were obtained with approximately 20% water (w/w). Results showed that the yield of analytes obtained with the natural deep eutectic solvent is similar to that of methanol. A high advantage of the use of natural deep eutectic solvent is their incapability to extract ginkgolic acids (considered very toxic to human) due to their low polarity and low dissolution in natural deep eutectic solvents. This method proved to be able to deliver reproducible chemical profiles from the natural deep eutectic solvent extracts (Liu et al. 2018).

Influence of deep eutectic solvent properties on the extraction efficiency

The properties of deep eutectic solvent highly influence the extraction efficiency (Tang et al. 2014). These properties depend both on the physico-chemical properties of each deep eutectic solvent component and on the interactions between the two constituents. The extraction efficiency is also influenced by the deep eutectic solvent solubilizing capacities and eventually its cell structures disruption ability. The water content, which is generally present in the extraction media when targeting bioactive compounds, also influences the extraction efficiency. In fact, the properties of deep eutectic solvent can be heavily modulated by the presence of water (El Achkar et al. 2019).

Melting point

As it was mentioned above, deep eutectic solvents are characterized by a lower melting point than that of any of its individual components (Zhang et al. 2012). Nevertheless, not all deep eutectic solvents are liquid at ambient temperature, and therefore the melting temperature is the first criteria to consider when choosing a given deep eutectic solvent for an extraction procedure.

Density

The difference in density values of deep eutectic solvents, which ranges from 1.041 to 1.63 $g.cm^{-3}$, is explained by their molecular organization and packing (Zhang et al. 2012). Deep eutectic solvent's density is a highly important property when separating phases in the extraction process especially in dispersive liquid–liquid microextraction techniques because most of the separation processes are based on the density differences between the two phases. Deep eutectic solvent's density decreases linearly when the temperature is increased as it was shown by Florindo et al. (2014). The molar ratio of the deep eutectic solvent components also heavily influences the density values (Wahaibi et al. 2019).

Viscosity

Most of the deep eutectic solvents possess high viscosity values (> 100 Cp) at room temperature (Zhang et al. 2012). This high viscosity is attributed to the presence of an extensive hydrogen-bonding network, Van der Waals and/or electrostatic interactions between the compounds that restricts the mobility of the free species inside deep eutectic solvent and restricts the dispersion of deep eutectic solvent in the extraction medium during the extraction process (Zhang et al. 2012; Habibollahi et al. 2018). Whereas high viscosity may be considered as favorable for the prevention of entrapped agents from vaporization, it hampers the mass transfer and thus produces lower extraction efficiency. Therefore, this problem can be solved by increasing the temperature, thus leading to a better penetration of the solvents in the sample; this is known as Arrhenius-like behavior (Bubalo et al. 2018). Also, adding a certain percentage of water to a deep eutectic solvent, at which the deep eutectic solvent's network is still maintained, is another way to decrease deep eutectic solvent's viscosity (Qi et al. 2015; Fernández et al. 2018). However, the addition of water can alter the hydrogen bonds between deep eutectic solvent and the target compound (Bajkacz and Adamek, 2017). Water-added deep eutectic solvents are more suitable for the extraction of polar compounds, whereas deep eutectic solvents with low water content are better for the extraction of nonpolar compounds (Dai et al. 2013a, b). Obviously, the nature of deep eutectic solvent components and the molar ratio also strongly influence the viscosity of a deep eutectic solvent (Abbott et al. 2011; Bi et al. 2013; Cao et al. 2018). Deep eutectic solvent with high viscosity may be selected for the single-drop microextraction techniques, because they facilitate the suspension of the drop at the end of the needle of a microsyringe.

Compatibility with instrumental detection systems

A high advantage of using deep eutectic solvent in the extraction techniques is the absence of interference generally observed for these solvents and their constituents with the detection methods. Many deep eutectic solvents showed a high compatibility with various instrumental detection systems such as mass spectrometry, flame ionization detector, UV–visible spectroscopy, diode-array-detector, graphite furnace atomic absorption spectroscopy, Fourier-transform infrared spectroscopy and fluorescence spectroscopy. Therefore, new combinations with advanced separation techniques like high-performance liquid chromatography, gas chromatography and thin-layer chromatography are ongoing, for example by using a certain percentage of deep eutectic solvent in the mobile phase (Tan et al. 2016).

Surface tension

Surface tension depends on the strength of intermolecular interaction of deep eutectic solvent and on temperature (Tang et al. 2014). Generally, most of the deep eutectic solvents have higher surface tension than conventional solvents. Deep eutectic solvent with low surface tension can be applied as an adhesive or wetting agent in the extraction techniques (Li and Row 2016).

Polarity and solubilizing properties

Deep eutectic solvent's polarity is an important parameter regarding its miscibility in other solvents or either in the sample solution, and regarding its solubilizing efficiency toward target analytes (Dai et al. 2013a, b). Deep eutectic solvents are known to have good solubilizing properties for polar and weak-polar compounds, including drugs, pharmaceutical ingredients, metal oxides, carbon dioxide, and elemental species such as lead, mercury and cadmium. (Aroso et al. 2016). Also, deep eutectic solvent proved better solubilizing effect, therefore better extractability compared to conventional solvents (Fernández et al. 2018). These properties may be rationalized, at least partially, by the "like dissolves like" theory, thus helping the choice of the adequate deep eutectic solvent regarding its polarity. Recently, deep eutectic solvents have been tailored to be target-specific via the selection of specific individual components based on the analytes via in silico methods. Unique interactions between the deep eutectic solvents with target analytes make it possible to selectively separate trace of this analyte from complex matrices (Fernández et al. 2018). It has to be mentioned that increasing the temperature generally leads to a decrease in the polarity of deep eutectic solvent because of the reduction in the hydrogen-bond donating acidity of the solvent, as observed

with choline chloride/glycerol deep eutectic solvent (Tang et al. 2014). A linear correlation has also been underlined between the choline chloride proportion and the polarity of the resulting deep eutectic solvent.

pH

The pH of deep eutectic solvent can affect the charge of the bioactive compounds subjected to extraction, and thus the extraction efficiency. In their neutral forms, analytes are generally much easier to be extracted by weakly polar solvents. Therefore, the pH of the extraction procedure should be higher than or near to the pKa values of the studied analytes (Mohebbi et al. 2018). The pH of different deep eutectic solvent changes differently with temperature, and their acidity is highly affected by the type of hydrogen bond donor (Tang et al. 2014). The highly polar molecules demand an acidic environment for a better extraction; therefore, organic acid-based deep eutectic solvents or some natural deep eutectic solvents are often the best choice. This was observed with organic acid-based natural deep eutectic solvents that showed the best extraction results for anthocyanin (polar compounds), while sugar-based natural deep eutectic solvents were a better choice for other phenolic compounds (Radošević et al. 2016). Finally, due to their amphoteric properties, the extraction of proteins is highly influenced by the pH, and accordingly their isoelectric point should be taken into consideration (Li et al. 2016).

Cell disruption ability

There is no doubt that some extraction techniques, such as ultrasonication, microwave extraction, as well as hot reflux extraction and others, cause cell disruption. However, the solvent used has an additional impact on the cell disruption. Using different extraction techniques followed by scanning electron microscope analysis, it was proved that deep eutectic solvents cause cell rupture more efficiently than conventional extraction solvents such as methanol and ethanol. This leads to the full release of the target analyte and its subsequent dissolution in the deep eutectic solvent (Chen et al. 2016; Jeong et al. 2017; Zhou et al. 2018; Wang et al. 2018).

Conclusion

Owing their low cost, easy synthesis, eco-friendly behavior and solubilizing capacities, deep eutectic solvents may be considered as suitable extraction solvents in the newly developed microextraction techniques. The use of deep eutectic solvent in many extraction techniques, either alone or mixed with a certain percentage of water, gives many advantages compared to the toxic conventional organic solvents. This was mainly proved by the enhanced extraction efficiency of different kind of molecules and macromolecules specially proteins and plant secondary metabolites. In addition, deep eutectic solvent properties, such as melting point, density, viscosity, compatibility with instrumental detection systems, surface tension, polarity and solubilizing properties, pH and cell disruption ability, should be considered for a maximum extraction efficiency. Consequently, these early twentieth century arisen solvents were immensely applied in the domains of chemistry given their special criteria; and as the selected publications in this review underlines, these solvents guarantee further progress in the domain of extraction.

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