Journal of Cleaner Production 380 (2022) 135147

Contents lists available at ScienceDirect

Journal of Cleaner Production

journal homepage: www.elsevier.com/locate/jclepro

Review

Review of deep eutectic systems from laboratory to industry, taking the application in the cosmetics industry as an example

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ARTICLE INFO

Keywords:
Deep eutectic systems
Extraction
Bioactives
Cosmetics
Green and sustainable chemistry

ABSTRACT

Green and sustainable chemistry principles have been employed in different industries to create greener and safer chemicals and processes, by replacing hazardous solvents with safer and more efficient ones. A state-of-the-art analysis on deep eutectic systems (DES) shows their consistent growth in the fields of chemistry, particularly as extraction solvents, mainly of bioactive compounds from natural sources. In this sense, a patent review was carried out, to highlight the relevance of DES, formed by natural compounds, in the cosmetic industry and the commercial added value of this technology at the industrial scale. Despite their good extraction efficiency, DES physicochemical properties need to be considered, as they may present some limitations in the process scale-up. This implies the study of several parameters, such as the cost of raw materials, the investment necessary to adapt or implement new equipment, energy consumption (for instance for pumping, heating, and stirring), and treatment of any by-products and wastes, in both the upstream and the downstream operations. Due to their inherent properties, DES can also be used as stabilizing agents of the bioactive compounds extracted, allowing their direct use in final products, namely in cosmetics, which is translated into a reduction of the downstream costs. This work further reports a case study of the extraction of grape anthocyanins with DES, and the necessary steps required to take this process from a laboratory scale to an industrial scale, targeting the cosmetic industry.

1. Introduction

In recent years, attention has been focused on improving the quality of life around the world. The Paris Agreements (PA) and the 2030 Agenda for Sustainable Development (ASD) are examples of such efforts. They both aim to bring a global partnership working towards ending poverty, reducing global warming, and preserving wildlife across all ecosystems. A viable solution to tackle some of the problems that were presented by both the PA and ASD is the use of green and sustainable chemistry (GSC), which covers at least ten out of the seventeen goals of the 2030 ASD, (goals 2, 3, 6, 7, 9, 11, 12, 13, 14, and 15). The implementation of GSC aims to revise and improve current chemical products and processes by reducing and/or removing the use of hazardous substances. In 1998 Anastas and Walker proposed the 12 principles of green chemistry (PGC), intended as a starting guideline when developing greener chemicals and processes (Principles of Green Chemistry, 2021). One of the most efficient ways to achieve greener processes is by replacing hazardous and inefficient solvents with safer and more efficient ones.

A class of solvents that fit these criteria are deep eutectic systems which will be explored throughout this work. The use of DES is discussed, concerning the benefits and challenges linked to its application in cosmetic industry, through a patent review, which seeks to address the difficulties of scaling up extraction processes, and a case study that emphasizes the potential environmental and economic impacts related to DES-assisted extraction of active compounds.

The aim of this review is to give a brief overview of the current knowledge regarding the use of DES as extraction solvents in a translation context, from a proof of concept in a laboratory setting to an industrial application, exploring future directions in designing efficient

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https://doi.org/10.1016/j.jclepro.2022.135147
Received 22 February 2022; Received in revised form 7 November 2022; Accepted 8 November 2022
Available online 11 November 2022

and sustainable extraction processes.

2. DES and their relevance to green and sustainable chemistry

DES are mixtures of two or more compounds, a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA), which, due to intermolecular interactions, when mixed in a certain molar ratio, suffer a large depression of their melting point, becoming a liquid at room temperature. Since they are formed through intermolecular interactions, mainly hydrogen bonding (Paul et al., 2017; Liu et al., 2018), there is usually no reaction taking place, meaning 100% atom economy and no waste production in the preparation. DES preparation is usually done by mixing the HBA and HBD at a certain molar ratio and stirring the mixture at elevated temperature (usually 60 °C), with no need for further purification steps (Smith et al., 2014; Pena-Pereira and Namieśnik, 2014). Due to these characteristics, DES preparation has an exceptionally low E-factor (ratio of waste produced per product formed), complying with several principles of green chemistry. The intermolecular interactions between the used HBA and HBD are responsible for the physicochemical properties displayed by DES, including low melting point, low volatility, nonflammability, low vapor pressure, acidity (Qin et al., 2020), tailor-made polarity, chemical and thermal stability, and miscibility (Zainal-abidin et al., 2017; Zhang et al., 2012).

DES are also able to easily solubilise compounds, such as phenolic compounds or active pharmaceutical ingredients, increasing their availability (Dai et al., 2013a; García et al., 2016). By changing the nature of the HBA:HBD or the molar ratio, it is possible to tune the physicochemical properties of DES, making them versatile solvents in different fields of applications, as seen in Fig. 1. A literature search on the Web of Science with the key words "deep eutectic solvents" demonstrated a substantial number of research fields (104 different fields and 6774 articles). Most of the categories represented in Fig. 1 belong to the field of Chemistry, with the most notable exceptions being: Multidisciplinary Material Sciences (6%), Energy Fuels (5%), Food Science Technology (3%) and Thermodynamics (3%).

As shown previously, DES have been used in a myriad of research fields, with diverse types of applications in mind, such as electrochemistry (Enrica et al., 2021), environmental chemistry (Malolan et al., 2021; Chen et al., 2021), and use as solvents (Cao and Su, 2021), biosensors (Svigelj et al., 2021), and lubricants (Donato et al., 2021), among others, with an emphasis on the study of their physico-chemical properties (Aroso et al., 2017; Paiva et al., 2014). However, this manuscript focuses on their use as a solvent for the extraction of versatile bioactive compounds (Kalyniukova et al., 2021), highlighting the use of these extracts for cosmetic products. Namely, DES have proven to be able to dissolve a wide array of compounds (García et al., 2016; Dai et al., 2013b), are easy to produce, can be safely handled, and can be tuned to selectively extract certain compounds (Rente et al., 2021; Ivanović et al., 2018). An example of DES tunability can be seen in Xu et al. (2019) and Cao et al. (2018) where DES polarity was tuned in order to increase the extraction yields of flavonoids. Other properties, such as DES ratios and composition, can also be tuned to increase extraction yields (Mansur et al., 2019; Ali et al., 2019).

Fig. 2 compiles data from around 650 articles, dealing with DES-assisted extraction of various compounds, most of which are phenolic compounds (50%), followed by metals, pesticides, proteins, and lignocellulosic materials. The number of publications has been increasing considerably since 2013, with an exponential growth.

Taking into consideration the interest in using DES as an extraction solvent, and the PGC to achieve green and sustainable processes, waste from the food and agricultural industries can be also used as a matrix to supply bioactive compounds of interest, creating new products of high-

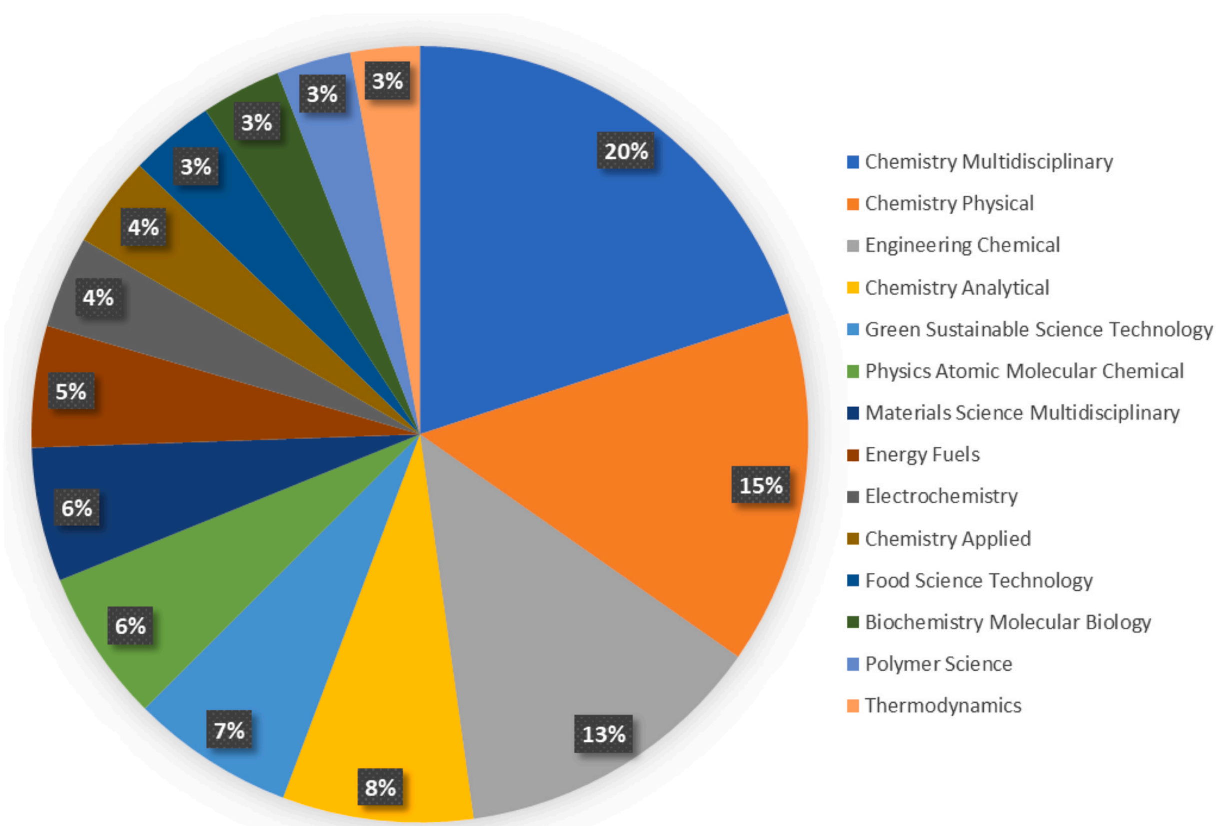

Fig. 1. Versatility of DES reflected by the number of articles published in various research fields (data available on Web of Science using keywords "Deep eutectic solvent" accessed on 07.12.2021).

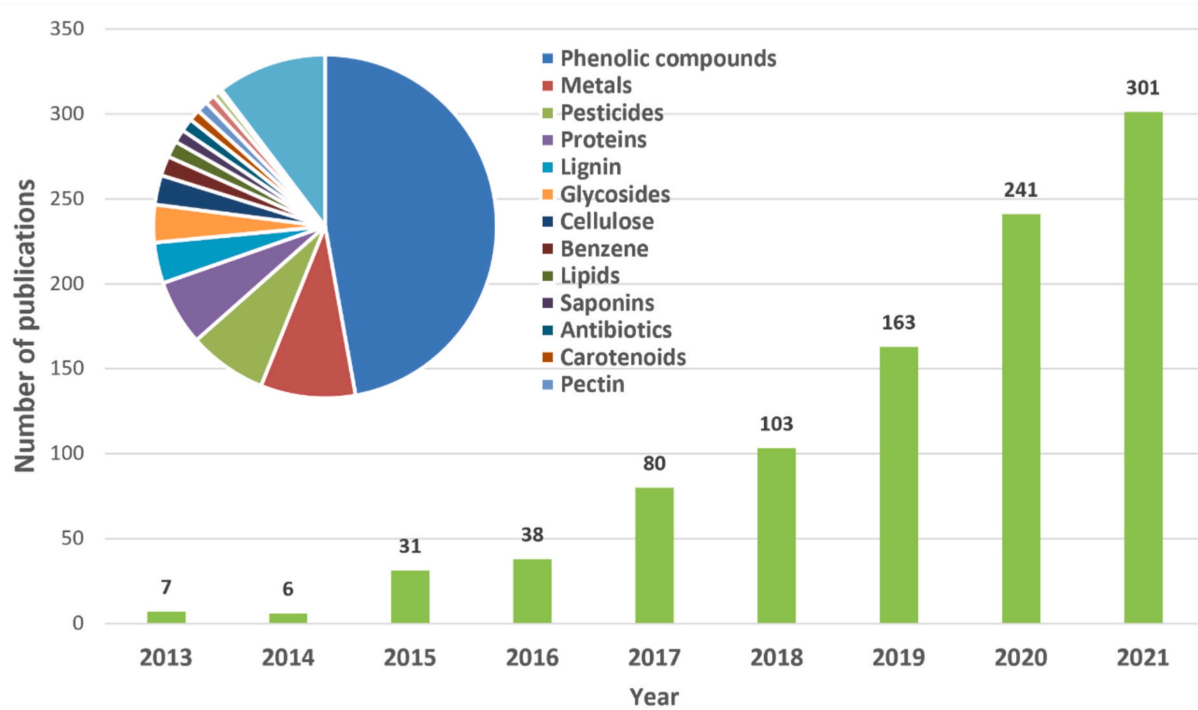

Fig. 2. DES-assisted extraction publications in the period 2013–2021 and distribution of original scientific articles according to the compound of interest (source: Web of Science).

added value.

These compounds are interesting due to their anti-inflammatory, neuroprotective, antimutagenic and anti-carcinogenic properties (Dai and Mumper, 2010) allowing them to be used in the production of cosmetics, pharmaceuticals, and nutraceuticals, as well as other food additives (Zainal-abidin et al., 2017; Viviane et al., 2019). A recent review by Wils et al. (2021) on the valorisation of biomass in France showed that research into DES used as extraction solvents follows similar steps: (i) DES, largely choline chloride based, are prepared and characterised, (ii) the biomass is prepared for extraction, (iii) extraction of bioactive compounds is conducted, (iv) extract properties, such as stability, phenolic content, antioxidant activity, and toxicological behaviour are studied, and then (v) a final formulation is discussed. The authors identified that the final formulation is often targeted towards the cosmetics industry, due to the advantageous properties of DES′, in conjunction with the extracted compounds and biomass valorisation.

This work intends to evaluate the use of DES for the extraction of phenolic compounds and the implementation challenges for the scale-up of the extraction process, using the extraction of grape anthocyanins as a case study (Panić et al., 2019a, 2019b).

3. Patent review

The relevance of the field for industrial purposes can be measured by the number of patent applications filled. A review of patented processes was herein conducted; patents were searched in worldwide.espacenet.com, and data was narrowed down using the following Boolean string: “deep eutectic” AND (solvent OR system) AND “extraction”. The first patent on the use of DES for extraction purposes (van Spronsen et al., 2011),was published in 2011, by Spronsen et al. (van Spronsen et al., 2011) (U.S. patent No.: US9441146B2) from the University of Leiden, Netherlands. Since then, about 24 patents on the topic have been published. From a geographical point of view, about 75% of patents applicants are based in China, with the rest 25% of applicants based in the Netherlands, the United Arab Emirates, the United States of America, and France, Fig. 3.

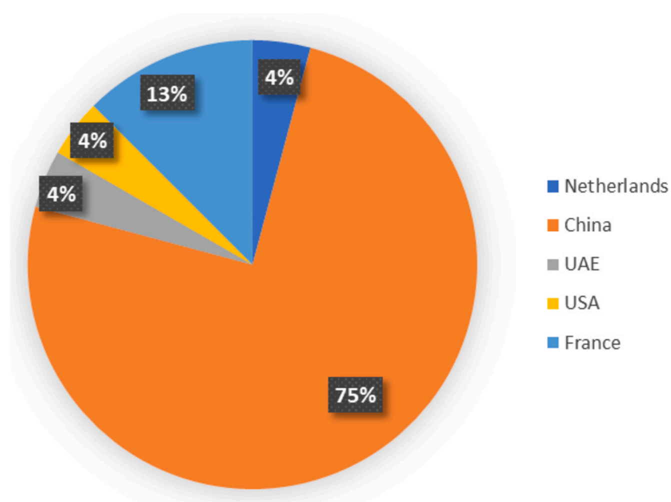

Fig. 3. Geographical distribution of patent applicants regarding DES and extraction methods.

It is important to note that most patent applicants are academic institutions such as universities, rather than industrial companies. The patents produced out of these academic institutions focus mostly on small and laboratory-scale methods and, therefore, the viability of the process at a pilot or industrial scale is not demonstrated. In terms of patents with direct industrial applications, Petcavich (2013) (Chinese patent No.: CN104130798A39) shows that it is possible to use a choline chloride urea-based DES to extract liquid hydrocarbons from oil rock. The patent describes a method that can be used at a smaller scale to process oil rock, either by heat and stirring processes or by microwave-assisted extraction, or at a larger scale by pumping the DES into the geological formations that contain oil rock to promote the extraction.

Peters et al. (2017) (Chinese patent No.: WO2019106406A1) describes a method for preparing a hydrophilic DES that can extract mercury from hydrocarbon feeds, as well as a method for recovering the mercury from the extraction mixture. A patent filled by Tran et al. (2020) from William Marsh Rice University, USA, (United States patent No.: US20200399737A1) discloses the possibility of recycling Li-ion batteries, using green chemicals and processes. This patent describes a method where DES are used to extract, recover and recycle metals from spent lithium-ion batteries and waste materials. It also shows that it is possible to recover the metal ions from the DES and to regenerate cathode materials using the recovered metallic ions.

Concerning the patents with industrial applicants, only three were published, and two of them were granted, Caprin et al. (2015) (French patent No.: FR3036618 B1), Charton et al. (2019) (United States patent No.: US10363212 B2), Lavaud et al. (2015) (French patent No.: WO2016162703 A1). Caprin et al. (2015) patent, entitled: “Extraits Vegetaux destines a la cosmetique, solvants et procedes pour les obtenir”, filed by Gattefossé S.A.S., described a method for the preparation of DES capable of extracting bioactive compounds from *Calendula officinalis*, complemented with cytotoxicity assays, as well the application of the DES/extract on a gel/emulsion for use in cosmetic products. This patent points out the drawbacks of commonly used extraction solvents in the industry, such as water (where additives such as microbiological stabilisers are needed), glycols (which present potential toxicity problems and a poor perception by end consumers), and ethanol (volatility makes transport and storage difficult), while presenting DES as an alternative. The DES described, composed of a mixture of polyols, sugars, and amino acids, can efficiently extract bioactive compounds, especially chlorogenic acid from *Calendula officinalis.* From the same applicant, Charton et al. (2019) patent, describes a method for the extraction of bioactive compounds from *Aesculus hippocastanum*, using DES. It describes methods to study the biological activities of the extracts and their incorporation into a cosmetic formulation.

Lavaud et al. (2015) patent, filled by Naturex, describes a method for the extraction of bioactive compounds from an array of matrices such as cherry blossoms, horsetail, plantain and saffron flowers, among others, using betaine-based DES for the formulation of different cosmetic, pharmaceutical and nutraceutical products. It also appears that these documents are related with cosmetic applications (classification A61K). At the end of this work, we will try to identify why cosmetic industry seems to take the lead in the adoption of DES at a larger scale. These patents describe different DES that can be used for the extraction of bioactive compounds of interest from vegetable matrices, detailing the DES preparation and the extraction methodology, while also providing data on the cytotoxicity of the DES/extract mixture.

Spronsen et al. (van Spronsen et al., 2011), from the University of Leiden, entitled “Process for extracting materials from biological material”, describes the possibility of using DES to extract a large amount of non-polymeric and polymeric compounds from natural sources such as plants, animals or micro-organisms.

Dalian University, China, filled a patent on a method for the preparation of a DES-supported liquid film, in a porous support, for the extraction of tryptophan Li et al. (2013) (Chinese patent No.: CN103357278A) and one method of extracting five types of mecamides in Maca by using DES Li et al. (2017) (Chinese patent No.: CN107748211A) Other works from China report a method for extracting anthocyanin from *Alnus elata,* by utilizing a deep eutectic solvent, as well as a purification method for the anthocyanins, with the application of a macroporous resin adsorption Lou et al. (2016a) (Chinese patent No.: CN105777696B). The IP behind the extraction of rutin, from *Sophora japonica*, using DES, was protected by the South China University of Technology. It includes a description of the preparation of the DES, extraction method and conditions, separation of the solid and liquid phase, and rutin purification Lou et al. (2016b) (Chinese patent No.: CN106046082A). Nanjing Forestry University, China, filled a series of patents based on the extraction of bioactive compounds (organic acids, cyanidins) from *Ginkgo biloba*, namely, “Deep eutectic solvent for synchronously extracting five organic acids from folium ginkgo and preparation method and extracting method thereof” Cao et al. (2017) (Chinese patent No.: CN107694147A); Su et al. (2017a) (Chinese patent No.: CN107759556A) and Su et al. (2017b) (Chinese patent No.: CN107789376A).

A method for the preparation of a DES for the extraction of cellulose from fruit and vegetable wastes, as well as a process for the esterification of the extracted cellulose, is disclosed by Bai et al. (2018) (Chinese patent No.: CN108611897A). Gao et al. (2019) (Chinese patent No.: CN110317156A) illustrates the preparation of a micro emulsion by mixing in a mass ratio: 10–50% DES, 45–80% composite surfactant (mixture of a surfactant and a co-surfactant in ratio 5:1–3:1), and 5–40% cyclohexane, to extract astaxanthin from shrimp shells.

The Tobacco Research Institute (TRI) of the Chinese Academy of Agricultural Sciences (CAAS) is the applicant of two patents on. Tan et al. (2018a) (Chinese patent No.: CN110698526A) describes a method for the ultrasound assisted extraction of isoflavones from freeze dried chickpea shoots. Tan et al. (2018b) (Chinese patent No.: CN110693939A) describes a method for the extraction of flavonoids from the money plant tree leaves.

China is proliferative in the production of IP. Rao (2019) patent (Chinese patent No.: CN110721206A) describes a method for the extraction of flavone from *Phellinus igniarius* (mulberry) using DES. Hong et al. (Hong and Tao, 2020) (Chinese patent No.: CN111116443A) protects a method for extracting a carotenoid by using natural deep eutectic solvents. Chen et al. (2020) (Chinese patent No.: CN111171095A) describes a method for the preparation of DES, useful for the extraction of flavone di-C-glycoside from *Premna Fulva*. The Institute of Bast Fiber Crops, Chinese Academy Of Agricultural Sciences, submitted an application related to the extraction of polysaccharides from *Ganoderma lucidum* Tan et al. (2020) (Chinese patent No.: CN111269328A). A method for separating and extracting lignin by *in-situ* synthesis of deep eutectic solvent is protected in a patent by Yang et al. (2020) (Chinese patent No.: CN112029115A), which aims the preparation and extraction of lignin using a DES. Yu et al. (2020) (Chinese patent No.: CN112125894A), from the Inner Mongolia University for Nationalities, discloses a method for green and efficient extraction of red clover isoflavones using natural DES.

The DES systems described in the patents, as well as the extraction method used and post-processing after extraction, are presented in Table S1. Details such as extractions conditions, mainly extraction time and temperature, are not considered in this table since they are quite broad. A large majority of the used DES contain choline chloride or quaternary ammonium compounds as primary components. Nonetheless, it is important to notice that the European Union regulations ban the use of choline chloride for cosmetic applications (Regulation (EC) No 1223/2009) (European Commission, 2009). As such, the information in these patents can be used as a starting point for the development of new products; for instance, when choline chloride can be replaced by other molecules with a similar behaviour in the formation of DES, like betaine, although clear comparisons cannot be made. This issue was already mentioned by, Caprin et al. (2015), Charton et al. (2019) and Lavaud et al. (2015), and the solution presented was, in fact, the use of betaine.

Ultrasound-assisted extraction method is often retrieved in the cited patents. While extraction efficiency is higher using ultrasound at laboratory scale, the scale-up of this technology needs to be deeper evaluated before being proposed as an alternative to the well-established heating and stirring method (Vilkhu et al., 2008).

Post-processing of the extractions always requires the separation of a solid phase and the desired liquid phase. To do so, filtration or centrifugation are typically employed. At this step, two approaches can be followed: (i) purifying the desired bioactive compounds into a crystalline form using chromatographic or adsorption methods or (ii) produce a ready-to-use DES/extract mixture. An advantage of creating ready-to-use extracts comes from the fact that extra purification steps are not needed, reducing the costs of the downstream processes (as discussed later). Furthermore, DES are known to be stabilizing agents, hence contributing to the preservation of the bioactive properties of the extracted molecules for longer time.

4. Engineering an extraction process from the lab to the industrial scale

In its simplest theoretical aspect, an extraction process consists in promoting the mass transfer of molecules of interest from a solid phase (e.g., plant raw material) to a liquid phase called the solvent. During the extraction process, two different major steps can be identified. The first one is the impregnation of the solid by the solvent, which can be performed by adequate stirring, and optimised by tuning different parameters, such as temperature or solid/liquid ratio. Except for highly viscous solvents, this step is generally quick, easy to scale up, and non-limitative for the process. The second step is the diffusion of the molecules of interest from the solid to the liquid phase according Fick's law. This occurring mass transfer depends on the nature of the solvent (e.g., density, polarity, volatility), and mostly rely on kinetic aspects (e.g., temperature and extraction time).

The cost factor of a process is an issue of major concern for the industries. Its evaluation encompasses the cost of raw materials, potential investments, energy consumption and treatment of potential by-products and wastes. In practice, an industrial extraction process cannot be designed without considering the upstream and the downstream operations. By upstream operations, we consider all sourcing activities of the solid phase (mainly from plant origin), from the cultivation field to the loading of the extraction reactor. Different aspects must be deeply explored and controlled, going from the way that the plant material is harvested (location, type of soil, reproducibility, industrial quantity projection, supplier's technical constraints) to the physical state of the raw material further extracted (drying, grinding, sieving, packaging, stability). On the other hand, downstream operations include the recovery of the liquid phase after extraction, the purification of extracted molecules and, eventually, the solvent regeneration.

Thus, an extraction process is a global multistep process, in which all unitary operations are interconnected. Even if some theoretical chemical engineering tools could help to define and optimise an extraction process, the design of an industrial extraction process requires a back-and forth strategy between different scales, Fig. 4.

Since the early stage of laboratory scale development, the economic viability of a process is evaluated considering the company's limitations (e.g., regulation, safety, environmental impact commitments). This implies anticipating and solving potential issues that typically appear during the scale-up development. The first obstacle that can hinder scaling up is an insufficient knowledge of the plant. Indeed, an effective sourcing strategy must include the industrial projection and future specifications to use the raw material in an industrial way. For instance, the particle size of a ground plant must be settled at laboratory scale, considering the extraction kinetic aspects and the feasibility of the solid/liquid separation step. Depending on climatic conditions, the phytochemical content of a plant raw material may vary between two crops. The best knowledge of the composition of extracted compounds is crucial to control the kinetics aspects and to determine the future specifications of the extract. This is usually an analytical challenge, but it is decisive to establish the toxicological profile of an extract.

The extraction conditions should be adapted during scale-up. Classically, laboratory reactors are made of glass but, when it comes to industrial ones, stainless steel is always preferred. The heating rate and the heat transfer are different and imply several adaptations of the process parameters. Technological choices, such as pump dimensioning or filtration technology and surface, are typically studied at the pilot scale. This scale is the cornerstone in the development of an extraction process, and allows the refinement of the estimates made at the laboratory scale, according to good manufacturing practices. Sometimes, fractioning or purifying an extract could be detrimental to the global biological activity of the crude extract (totum extract). In this case, the optimization of the process is guided through a compromise between the content of the main phytochemical families identified and biological activity assays. This is typically the case in the cosmetic industry, where biological and chemical extraction processes' guidance is carried out in parallel.

To sum up, all extraction processes represent a scale-up challenge mostly dependent on the raw material/solvent pair. When it comes to scaling up a DES extraction process, viscosity is the main issue. Mixing, transporting, and filtering a DES or extract is certainly more complicated than for conventional solvents. Thus, the potential benefits and transition to eco-extraction brought by DES solvents are accompanied by other challenges related to their industrial implementation.

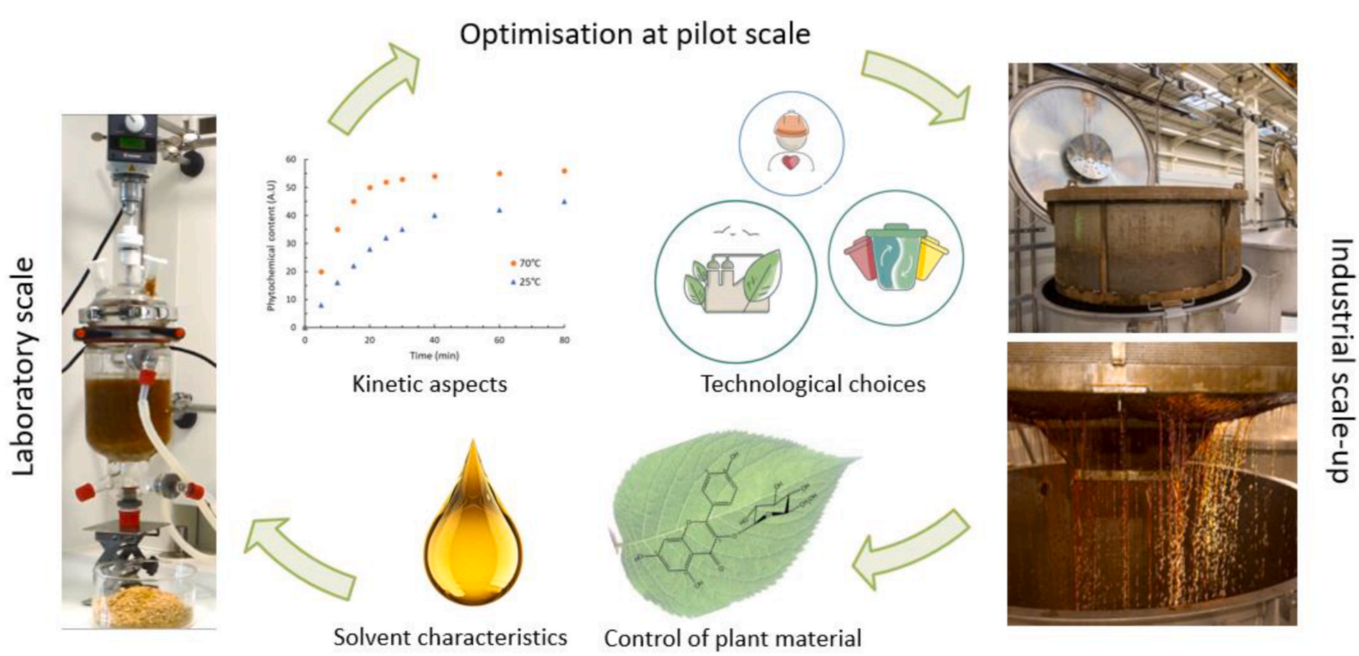

Fig. 4. Engineering a plant extraction process: a back-and-forth strategy between different scales.

5. Challenges related to industrial-scale applications of DES

Non-volatility and non-flammability (process safety), non-toxicity and biodegradability (human safety and environmental protection), and solvent-free preparation from broadly available natural raw materials are intrinsic properties of DES, which earned them the attribute “environmentally friendly”. On the other hand, their tunability allows the creation of perfect systems for solubilization and, consequently, extraction of practically any biomolecule. However, the choice of a DES for a particular process should be made carefully, keeping in mind the final product, followed by the design of the process, to meet the economic and environmental requirements.

5.1. DES properties in the context of industrial application

The most salient feature of DES is the ability to design an optimal one for a particular purpose. While the variety of DES is extremely beneficial, it makes selection difficult and time-consuming. This search can, sometimes, be simply governed by experience and data available in the literature, but could also be aided using computational methods. Looking at the DES application at industrial level, besides extraction efficiency, there are several other DES properties (e.g., viscosity, corrosion activity, environmental impact and price) that need to be considered in the search for the so-called ideal DES (Fig. 5). In the last 5 years, the influence of the structure of the DES on extraction efficiency has been thoroughly studied. Therefore, the focus here is only on the challenges associated with the selection of these solvents, in the context of industrial application.

The key concern of DES application at the industrial level is their relatively high viscosity (Mitar et al., 2019). Moreover, the viscosity of the solvent, not only affects the efficiency of the extraction due to low mass transfer, but also raises additional challenges in equipment design, and increases the energy requirements for agitation and pumping. The viscosity of DES is highly dependent on the components that make it up. For example, sugar- and acid-based DES are more viscous than polyol-based ones. DES viscosity is also a function of temperature and water content; therefore, viscosity can be easily lowered by running the process at higher temperatures, or adding water to the system. For example, for the DES choline chloride:urea (1:2 mol), increasing the temperature from 293.15 K to 323 K resulted in a 10-fold decrease in solvent viscosity (Abbott et al., 2004), while adding water to DES from 10 to 50% (w/w) could decrease viscosity by several orders of magnitude (Mitar et al., 2019). However, it should be kept in mind that the addition of water could lead to the weakening of hydrogen bonds between the components and, consequently, to the loss of DES supramolecular structure and extraction capacity (Dai et al., 2015).

To transfer DES from scientific concepts to practical applications, the corrosive activity of DES could be detrimental when in contact with various metals (Rublova et al., 2019). Indeed, the pronounced corrosive effect of choline chloride-based DES containing oxalic acid as a hydrogen bond donor on steel was confirmed, with a corrosion rate of 176 μm yr^{-1} (Amin et al., 2007). On the other hand, choline chloride-based DES with urea and ethylene glycol showed very low corrosion rates on steel, nickel, and aluminium, even when DES contained water. It was also observed that the addition of water to DES could affect the corrosion activity of metals. However, the influence of water content on the corrosive activity of the solvent was not found (Mitar et al., 2019).

Regarding the DES ecological footprint, DES generally show low to moderate toxicity toward bacteria, fungi, plants, animals (vertebrates and invertebrates) and various animal cell lines (Mbous et al., 2017; Radošević et al., 2015a). It appears that the pH value of DES is the most important DES characteristic affecting its toxicity. This means that DES, which contain organic acids such as HBD (e.g., oxalic, citric, malic, or

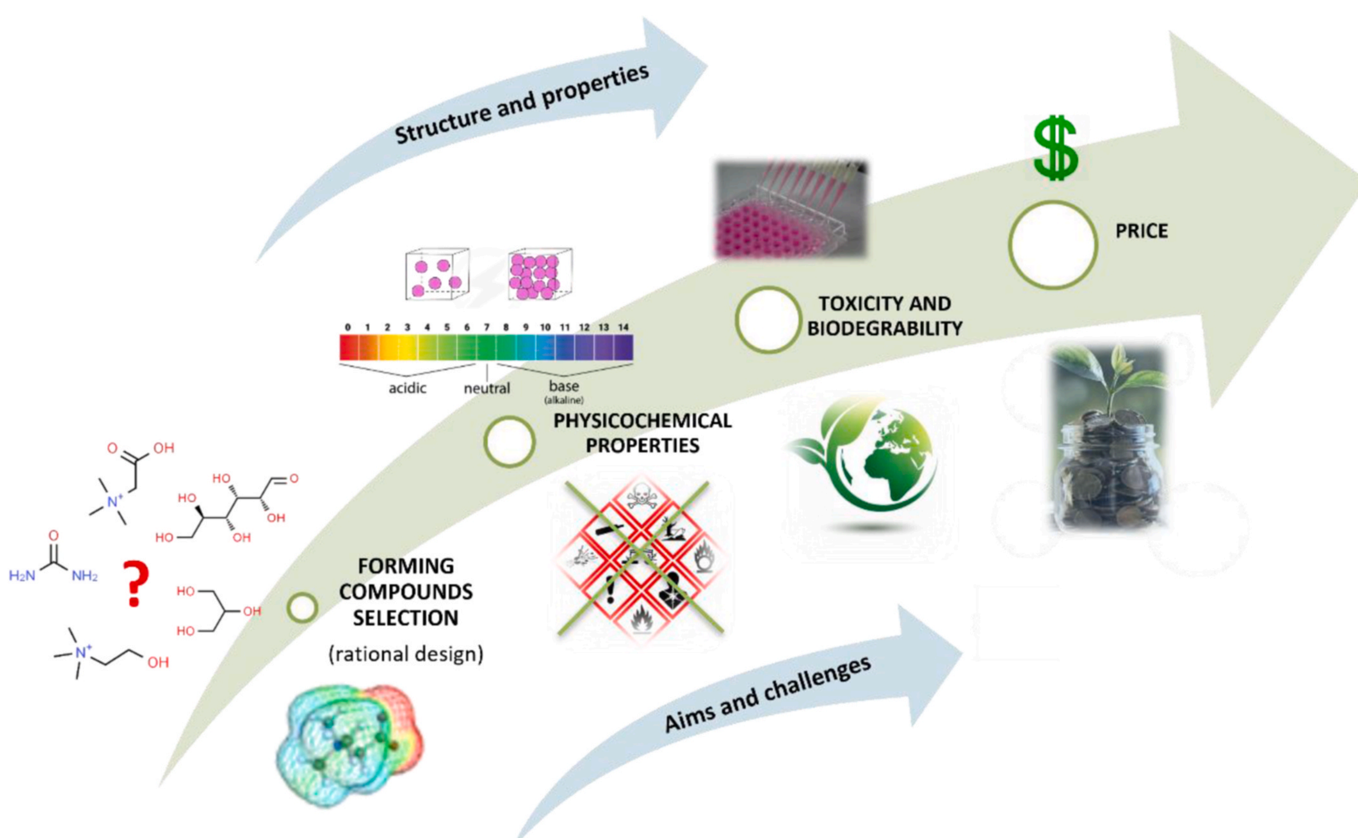

Fig. 5. Design and selection of DES for industrial application.

tartaric acid) are moderately toxic (Paiva et al., 2014; Radošević et al., 2016). On the other hand, DES which consist of choline, sugars, and polyols are less toxic, possibly because these ingredients are essentially required for cellular metabolism and the cells have a higher tolerance to them. In addition, the high viscosity of DES is often thought to be associated with increased lethality (Radošević et al., 2015b). Several authors reported that DES, which were produced from natural metabolites, could be classified as "biodegradable", according to OECD guidelines (Radošević et al., 2015b; Torregrosa-Crespo et al., 2020). However, DES based on choline chloride were more biodegradable than those based on choline acetate, while the DES with urea and acetamide, as the hydrogen bond donors, were more susceptible than those with glycerol and ethylene glycol.

The economic evaluation of DES showed a large price difference depending on their primary components, with an average price ranging from €7 to €100 kg^{-1}, which is comparable to organic solvents. For example, the cost of DES choline chloride: ethylene glycol at a molar ratio of 1:2 is about €65 kg^{-1}, while malic acid:glycerol at a molar ratio of 1:1 with 25% (v/v) water is €18 kg^{-1} (Panić et al., 2020). DES with amino acids are more than 20 times more expensive than those with sugars as hydrogen bond donors (Panić et al., 2017, 2019a). These substantial price differences in DES imply that the final decision on the choice of solvent should also be based on these criteria.

At this point, it should be noted that it is usually difficult to predict which DES, and at what water content, would result in an effective DES, and which crucial solvent properties would come into play. However, there are a large number of publications reporting DES' physical, thermal, chemical or biological properties, that can be used as a guide for selecting an ideal DES for a particular purpose. Moreover, an online collection of the physicochemical properties of DES is available, free of charge, for both academic and industrial researchers (Database@dessolutio), whose main objective is to collect information from scientific peer-reviewed publications on the experimental study of the physicochemical properties of DES. Finally, in-silico methods for predicting the properties of DES have recently been developed, leading to more informed DES selection decisions than the previous "trial and error" procedure (Wojeicchowski et al., 2020; Milani et al., 2020).

5.2. To purify, or not to purify, that is the question: downstream vs ready-to-use extracts

Since DES have a very low vapor pressure, isolation of the biologically active compounds is one of the major challenges for their industrial application (Panić et al., 2019a; Jeong et al., 2015). Therefore, it is questionable whether there is a need, and whether it is financially viable, to purify the compound(s) of interest from DES-based extracts, as DES could be considered safe for use. Jeong et al. (2017) were among the first to suggest that DES could serve as a multifunctional extraction, and storage medium, for bioactive natural cosmetic or pharmaceutical products for use on the skin, being itself an active ingredient. The components of DES are abundant in nature and are part of our daily diet, as well as a dietary supplement already on the market (e.g., choline, citric acid, betaine, amino acids, etc.); so, it is expected that the extract obtained by DES can be directly used in food, pharmaceutical, cosmetic and agrochemical products as ready-to-use extracts (Dai et al., 2013a). Moreover, when ready-to-use DES extracts of biologically active compounds are considered, the contribution of DES to the stability and biological activity of the extract should also be considered (Panić et al., 2019b; Torregrosa-Crespo et al., 2020). For example, the acidity of organic acid-based DES promotes anthocyanins stabilisation, and it seems that this stabilisation effect is related to the interactions between anthocyanins and DES-forming compounds, especially through hydrogen bonds (Panić et al., 2019c). Moreover, plant extracts based on DES have a different and usually higher biological activity than extracts obtained by conventional methods (Panić et al., 2019b; Grillo et al., 2020), due to the specific and unique profile of bioactive compounds in the DES extract. Also, DES have been shown to enhance the antioxidant activities of the obtained plant extracts, due to the reactive oxygen species scavenging DES itself, or the DES forming compounds (Nam et al., 2015); thus, it is expected that such natural extracts could serve as product preservatives, even better than the currently known antioxidants (Durand et al., 2017). Finally, based on reported DES antibacterial activity (Radošević et al., 2018; Wikene et al., 2017), DES-based ready-to-use extracts might also be less susceptible to microbial contamination.

However, if the goal is to obtain a purified extract that is free of solvents, other methods must be coupled with extraction to obtain a particular compound from DES-based extracts. These are, for example, (i) liquid-liquid extraction, (ii) solid-liquid extraction with microporous resin, and/or (iii) addition of antisolvent. Isolation of bioactive components by liquid-liquid extraction usually requires the use of hazardous volatile organic solvents (e.g., n-hexane, n-heptane, toluene, diethyl ether, etc.), but recent works have been able to overcome this, reporting the use of green agro-solvents (e.g., ethyl acetate, 2-methyl tetrahydrofuran, ethyl lactate, etc.) (Chemat et al., 2019). After liquid-liquid extraction, DES can be easily reused for another process cycle. On the other hand, high consumption of aprotic solvent, and low solubility of some species (e.g., polyphenols) in aprotic solvent, can be expected (Ruesgas-Ramón et al., 2017). The second most common method used at the laboratory scale for purification of bioactive compounds is solid-liquid extraction, using various macroporous resins as solid phase. The principle of this method is the adsorption of compounds from the extract to the macroporous resin, elution of DES with water, and desorption of compounds with an appropriate solvent (Ruesgas-Ramón et al., 2017). The third method described in the literature to obtain the product from the extracts of DES is its precipitation by the addition of antisolvent. The solubility of DES in polar solvents (ethanol (EtOH), water, etc.) allows complete dissociation and solubilization of the DES-forming components, leading to precipitation of the solubilized bioactive compounds and allowing their recovery after filtration, while consequent evaporation of the filtrate allows the restoration of the original DES structure (Ruesgas-Ramón et al., 2017). The possibility of reusing DES with high yield (~10% less yield than that of freshly synthesised DES), in at least 3 cycles, as well as the recycling yield of DES (~60–90%, depending on the recycling method used) was reported (Panić et al., 2019a).

Based on the above, the preparation of ready-to-use extracts, without additional purification of the extracts, seems to be an excellent opportunity, both from the technological point of view and from the aspect of product quality. Extracts prepared in this way, not only imply a simpler purification process, but also exert a unique phytochemical signature and biological activity, and could have a longer shelf life. However, it should be mentioned that binding guidelines and laws should be established in terms of when and how these ready-to-use extracts are safe for human consumption. Finally, if the purified product is the final goal, existing and well-established downstream methods could be easily applied, and what is also important, DES could be successfully recycled and reused.

5.3. Greenness and sustainability of DES-assisted extraction processes

It is widely argued that DES contribute to improved environmental performance and sustainability of certain processes, due to its green attributes. Also, the lack of a thorough understanding of DES process parameters is a major challenge in convincing investors to establish a commercial DES-based industrial process. Therefore, to encourage the use of these solvents in new or existing industrial processes, a more holistic approach needs to be taken that considers economics (the cost of DES, capital investment and utility costs), specially designed equipment for pumping and mixing viscous fluids, the complexity of product isolation (especially due to the non-volatility of these solvents), and DES reusability.

To the best of our knowledge, to date there is no study addressing the techno-economic evaluation of the DES-assisted extraction process to obtain biologically active compounds intended for the cosmetic industries. However, some important conclusions from the DES-assisted process for biorefinery of agricultural residues, and biogas production, could be a reasonable guide for evaluating the economic feasibility of the said process. For example, Kumar et al. (2020) found that focusing on increasing the number of high-value and low-volume products, instead of low-value and high-volume products, can significantly improve the economics of a DES-based biorefinery of lignocellulosic agro-residues. Also, recycling and reuse of solvents for subsequent operations reduces the share of raw materials in operating costs by up to 65%, which means that DES reuse is mandatory. As for the evaluation of the environmental friendliness of a given DES-assisted process, López et al. (2020) showed that DES-assisted extraction of free selenium amino acids, from lyophilized and powdered milk samples, leads to a significant reduction in the use of hazardous reagents, energy and generated waste, compared to the conventional method.

The lack of a techno-economic and environmental assessment of DES-assisted extraction of biologically active compounds led us to perform a rapid and simplified evaluation of the sustainability and costs of this kind of extraction process, in relation to a conventional extraction procedure, using the extraction of anthocyanins from agricultural waste (grape pomace) as a case study (Panić et al., 2019a, 2019b), Fig. 6. For this purpose, industry-accepted factors describing the sustainability of a process were calculated ($V = 0.1\ dm^3$), that is the ratio of the weight of generated waste to the total weight of the end product (E-factor), E-factor multiplied by an environmentally hazardous quotient (EQ), and the ratio of the total mass used in a process and the mass of the end product (PMI) (Paul et al., 2017). Additionally, for process greenness evaluation, we applied a simple, recently developed user-friendly metric: the complementary green analytical procedure index (ComplexGAPI (Płotka-Wasylka and Wojnowski, 2021)). Finally, a simplified techno-economic evaluation of the DES-assisted and conventional processes was carried out.

As can be seen in Fig. 6, the central part (i.e., extraction) of both the conventional and DES-assisted processes, was performed in the same manner (mixing at room temperature for 2 h), but the processes differed significantly in the complexity of downstream processing. In the conventional extraction process, the solvent was removed after extraction by reduced pressure and an unpurified solid anthocyanin extract was obtained. In the DES-assisted process (using chloride:citric acid with 30% water (w/w)), the obtained extract could be directly prepared as ready-to-use (Scenario 1), or the extracts could be purified by adsorption chromatography, to obtain anthocyanins as a crude extract (Scenario 2).

As can be seen in Table 1, the production of the ready-to-use extract

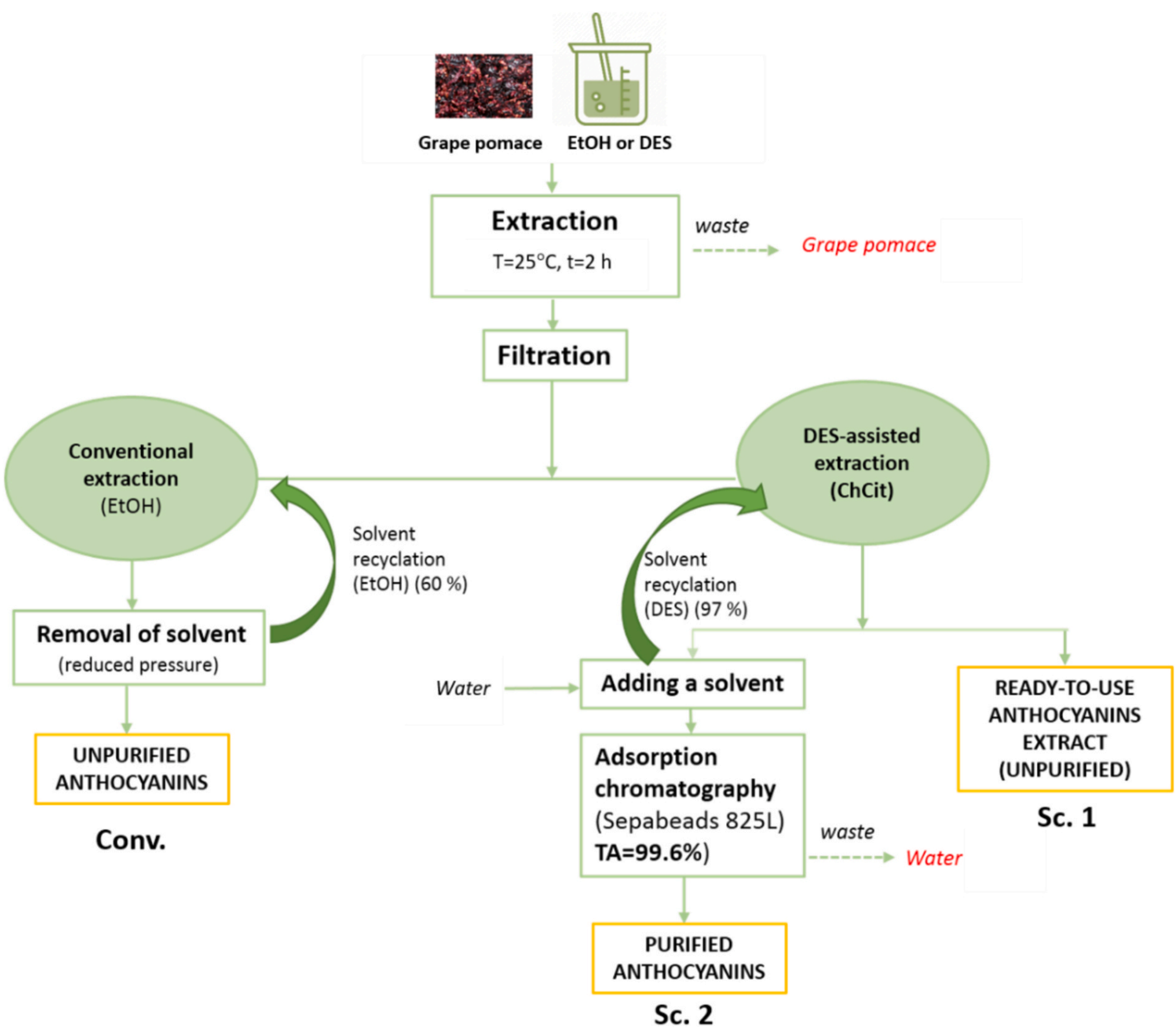

Fig. 6. Scheme of the extraction of anthocyanins from grape pomace, by using conventional solvent and the DES choline chloride:citric acid with 30% of water (w/w) as a case study. For DES-assisted extraction, two scenarios were considered: Scenario 1 (Sc 1.) where DES extracts were directly prepared as ready-to-use, and Scenario 2 (Sc. 2) where purification of anthocyanins was considered. The central part of the process (extraction) was the same for each process.

Table 1
Green credentials (0.1 L – scale) and cost estimation (50 L – scale) of conventional (EtOH-assisted) and DES-assisted extraction of anthocyanins.

TARGET PROCESS	Yield (mg g^{-1}dw)	E-factor[a] (kg mg^{-1})	EQ[b] (kg mg^{-1})	PMI[c] (kg mg^{-1})	Capital investment[d] (€)	Annual operating cost[d] (€)
Conventional extraction	0.9	11.1	11.1	38.2	570000	190000
DES-assisted extraction (ready-to-use extract, Scenario 1)	0.9	0	0	38.2	450000	170000
DES-assisted extraction (complete purification of the product, Scenario 2)	0.9	38.2	0	75.2	657000	240000

[a] The ratio of the weight of generated waste to the total weight of the end product (grape pomace as an industrial waste not included).
[b] E-factor multiplied by an environmentally hazardous quotient.
[c] The ratio of the total mass used in a process and the mass of the end product.
[d] Estimated by SuperProDesigner: capital costs were estimated according to the cost of equipment, installation, process piping and instrumentation; annual operating costs were estimated by material costs and utilities; the software in its library contained all the necessary equipment models, unit operations and chemical compounds (only data for DES were registered as a new compound); the costs of all featured conventional equipment, material and energy balances, as well as the calculation of electricity requirements, were obtained by the software and its default values in the database, and used for the calculation of investment cost and operation cost.

DES (Scenario 1) led to the lowest sustainability factors, as no waste was generated (E-factor and EQ values of 0 kg mg^{-1}), suggesting excellent sustainability. On the other hand, if product isolation is considered (Scenario 2), the E-factor and PMI increase significantly (38.2 and 75.2 kg mg^{-1}, respectively), leading to higher values than for the conventional process (11.1 and 38.2 kg mg^{-1}, respectively). This was a direct consequence of a more complex purification procedure of a DES-assisted process, where a significant amount of water was consumed (for dilution of the extract prior to adsorption chromatography). However, considering the environmental impact of water as waste generated (environmental hazard quotient equal to 0), EQ in the DES-assisted process was 0 kg mg^{-1}, while in the conventional process EQ = 11 kg mg^{-1}.

Furthermore, the greenness of the three extraction scenarios was assessed and juxtaposed using the Complex GAPI tool, represented with five pentagrams and an additional hexagonal field corresponding to process yield, conditions used, accordance with green economy principles, type and quantity of reagents and solvents used, instrumentation

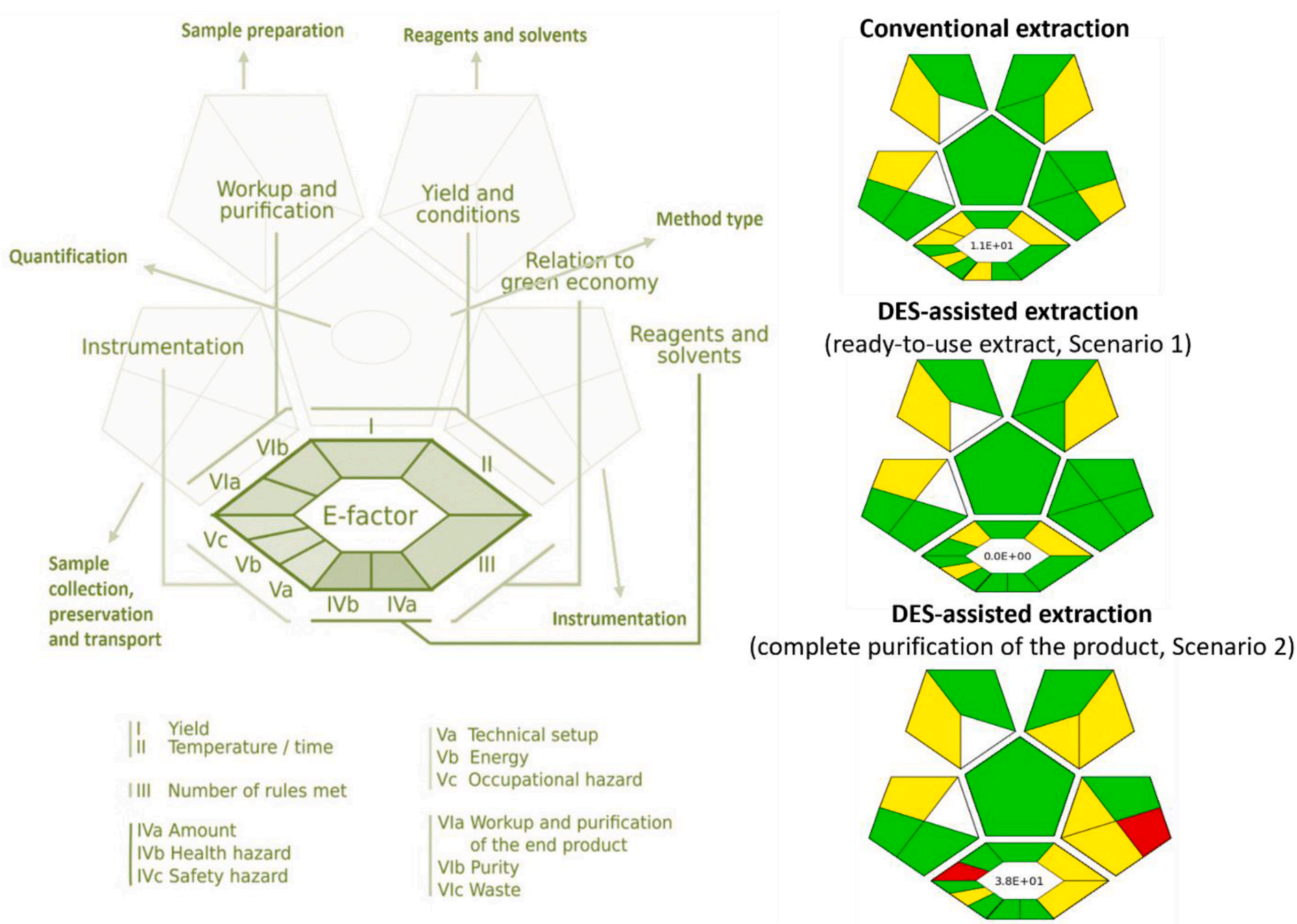

Fig. 7. Evaluation of conventional (EtOH-assisted) and DES-assisted extraction of anthocyanins, using ComplexGAPI tool (Płotka-Wasylka and Wojnowski, 2021). Pictograms were drawn by a freeware software available at: https://mostwiedzy.pl/en/justyna-plotka-wasylka,647762-1/complexgapi (red fields indicate steps that may be hazardous to the environment, yellow fields indicate steps with medium environmental impact, and green fields reflect eco-friendly steps).

used, and complexity of workup and purification (Płotka-Wasylka and Wojnowski, 2021). This metric was originally developed to evaluate analytical procedures, therefore slight adjustments to the methodology had to be made to appropriately rate different procedures for anthocyanins extraction (e.g., rating purity of the product, amount of solvent used, and energy consumed). By comparing the five pentagrams and a hexagonal field of the extraction methods, Fig. 7, DES-assisted preparation of ready-to-use anthocyanins extract (Scenario 1) proved to be the eco-friendliest, which concluded with 17 green regions (eco-friendly step), compared to 14 and 12 green regions for conventional extraction and DES-assisted extraction followed by anthocyanins purification (Scenario 2), respectively Table 1. Additionally, only extraction in Scenario 2 resulted in two steps potentially hazardous to the environment (fields coloured in red), related to advanced purification methods (adsorption chromatography) and waste generated during anthocyanins isolation from DES-based extract (contaminated water that is difficult to recover in a pure enough form for reuse), assigned as red regions in the pictogram. As for conventional extraction and preparation of ready-to-use DES-based extracts, the DES-based process was superior in terms of waste generation (completely waste less production), workup and purification (no purification required), and safe chemicals.

The economic evaluation was performed by using standard calculations and the development of a process simulation model designed using SuperPro Designer® (Ochoa et al., 2020). To make a comparison of simulated technologies at an industrial scale, the processes were scaled up to 50 L extractor capacity (the process yields and extract compositions at the industrial scale were presumed to be the same as at the laboratory scale). The conditions for each operation unit were based on works published by Ochoa et al. (2020) and Adeyl et al. (Adeyi et al., 2021). As shown in Table 1, the lowest investment cost (equipment, installation, process piping and instrumentation), and operating costs (material cost and utilities), were obtained for the DES-assisted process in Scenario 1, which was a direct consequence of the elimination of downstream operations, especially compared to DES-assisted process in Scenario 2, where complex procedures are required for DES removal before further use of the extract. These differences were especially evident within the capital costs (equipment, installation, process piping) of the three compared processes.

Overall, this rough economic and environmental assessment showed that the DES-assisted extraction of anthocyanin crude extracts led to slightly higher ecological impacts, higher capital investments and higher operating costs of the extraction process at a larger scale. However, switching from a process that involves product isolation to one that yields ready-to-use extracts, has a positive impact on the process sustainability. Considering the previously discussed advantages of ready-to-use extracts based on DES (product stability, higher biological activity, no microbial contamination, etc.), this approach represents an excellent option to produce high-quality plant extracts for use in the cosmetic industry.

6. Application of the extracts - why the cosmetic industry is taking the lead in the adoption of DES at larger scale

Despite a large number of patents concerning plant extraction with DES, only a few have been applied by industries and, among them, the cosmetic industry seems to be the most active. This raises the question of why the cosmetic sector is taking the lead in the wider adoption of DES. The first element of the answer is based on the regulatory and societal context of this type of industry. Indeed, personal care active ingredients must comply with a restrictive regulatory framework, but also meet various growing requirements in terms of naturalness, and environment and biodiversity preservation (Benoit et al., 2021). In short, the safety orientation of the benefit/risk balance in the cosmetic industry has been seen as a limitation to creativity for years, but is becoming a major source of technical innovation. For more than 10 years, the development of bio-based extracts for cosmetic ingredients has followed a "green revolution" of practices and brought a technological shift towards eco-extraction. Furthermore, mandatory environmental issues are, nowadays, supplemented by all the themes of corporate and social responsibility.

The cosmetic industry seeks to promote the sensible use of renewable raw materials through an efficient sourcing strategy. For example, the upcycling of by-products from the food industry is gaining momentum. The use of safer extraction processes is also encouraged, and the use of green and biobased solvents has become the main priority. The number of extraction solvents to perform plant extraction in the cosmetic field has shrunk with increasing sustainable requirements. Thus, DES systems rapidly appeared as a promising opportunity to bring innovation and novelty. DES possess low melting point, low volatility, nonflammability, low vapor pressure, and chemical and thermal stability; so, they constitute appealing candidates to perform plant extraction at industrial scale. Moreover, its physicochemical properties are maintained after extraction, and generate stable and easy to handle viscous liquid extracts. Thus, the use of purification or stabilizing techniques is avoided, and the global cost of the process is positively impacted.

Another aspect concerns the plant extraction performance of DES, in comparison with conventional solvents. Quickly, it appears that such new solvents bring opportunities to revisit well-known plants and obtain extracts with a unique phytochemical content. These crude (totum) extracts had shown a good compatibility with skin cells and the biological efficacies were detected regarding several classical cosmetic claims (moisturising, anti-aging, blue light protection) as shown in patents by Lavaud et al. (2015), Charton et al. (2019) and Caprin et al. (2015). Furthermore, the use of NaDES extracts in cosmetic is driven by the hydrogen bonded structure of these solvents. Indeed, a cosmetic formulation contains a large amount of water. When a NaDES extract is poured into a water-based formulation, the hydrogen bonded structure of the NaDES is disrupted, leading to the spread of active ingredients within the formula. Considering that an active ingredient represents less than 5 wt% of a cosmetic product, a liquid and ready to use NaDES extract can be added to all types of formulations, without dramatic changes of rheological properties or sensorial profile.

7. Conclusions and perspectives

Recent trends in the extraction of valuable plant metabolites, in the context of cosmetic industry techniques, have largely focused on finding solutions that enable the achievement of high-quality extracts, with boosted biological activity and long shelf-life, while trying to minimise the use of harmful solvents during the production process. The use of DES, as a new class of green solvents with exceptional structural flexibility, provides the opportunity for rational solvent design, in order to meet the requirements of the cosmetic industry in the production of truly natural and safe plant extracts. By performing a greenness and sustainability assessment of DES-based extraction of plant metabolites, we have shown herein that the production of ready-to-use DES-based extracts, both upstream and downstream processes, can be advantageous compared to the conventional extraction methods in terms of environmental sustainability and process cost. To summarise all the advantages and disadvantages of DES-assisted extraction of natural bioactive compounds for use in cosmetics, and to stress the perspective of the presented approach as well, we have applied a common tool used in strategic planning -Strengths, Weaknesses, Opportunities, Threats (SWOT) analysis Fig. 8. Strengths and opportunities of DES-assisted extraction (i.e., process according to green chemistry principles, economic feasibility without high capital expenditure, the discovery of new properties of well-known plants due to the unique phytochemical signature of DES-based extracts) give us a clear insight into why producers of cosmetic bio-based active ingredients identified the potential of DES to overcome the constraints they have to face. Research and development efforts can lead to the appearance of brand-new DES-based extracts, that are in line with the regulatory and societal context of the

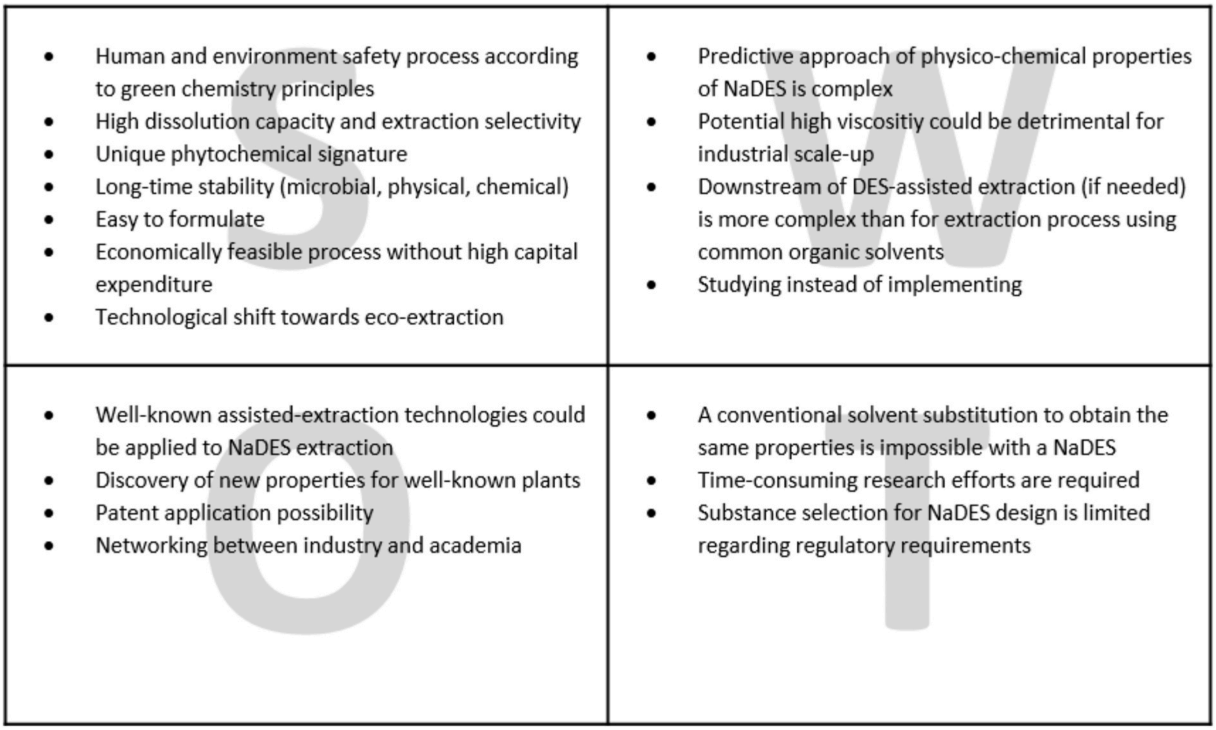

Fig. 8. Strengths, Weaknesses, Opportunities, Threats (SWOT) analysis of DES-assisted extraction of natural bioactive compounds for use in cosmetics.

cosmetic industry, without compromising safety and biological efficacy.

Declaration of competing interest

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

Data availability

Data will be made available on request.

Acknowledgments

This works results from the network collaboration under the frame of the COST Action CA 18224- Greenering, funded within the EU Horizon 2020 Programme. The work further was supported by the European Union through the European regional development fund, Competitiveness and Cohesion 2014–2020 (KK.01.1.1.07.0007) and the European Research Council (ERC) - under grant agreement No ERC-2016-CoG 725034. The project also received funding from national funding bodies, namely the Croatian Science Foundation (Grant No.7712), the European Union through the European regional development fund, Competitiveness and Cohesion 2014–2020 (KK.01.1.1.07.0007.) and by the Associate Laboratory for Green Chemistry (LAQV) which is financed by national funds from FCTFCT/MCTES (UIDB/50006/2020).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclepro.2022.135147.

References

Abbott, A.P., Boothby, D., Capper, G., Davies, D.L., Rasheed, R.K., 2004. Deep Eutectic Solvents Formed between Choline Chloride and Carboxylic Acids : Versatile Alternatives to Ionic Liquids, pp. 9142–9147.

Adeyi, O., Adeyi, A.J., Oke, E.O., Okolo, B.I., Olalere, A.O., Otolorin, J.A., Taiwo, A.E., 2021. Techno-economic and uncertainty analyses of heat- and ultrasound-assisted extraction technologies for the production of crude anthocyanins powder from Hibiscus sabdariffa calyx. Cogent Eng 8. https://doi.org/10.1080/23311916.2021.1947015.

Ali, M.C., Chen, J., Zhang, H., Li, Z., Zhao, L., Qiu, H., 2019. Effective extraction of flavonoids from Lycium barbarum L. fruits by deep eutectic solvents-based ultrasound-assisted extraction. Talanta 203, 16–22. https://doi.org/10.1016/j.talanta.2019.05.012.

Amin, M.A., Abd El-Rehim, S.S., El-Sherbini, E.E.F., Bayoumi, R.S., 2007. The inhibition of low carbon steel corrosion in hydrochloric acid solutions by succinic acid. Part I. Weight loss, polarization, EIS, PZC, EDX and SEM studies. Electrochim. Acta 52, 3588–3600. https://doi.org/10.1016/j.electacta.2006.10.019.

Aroso, I.M., Paiva, A., Reis, R.L., Duarte, A.R.C., 2017. Natural deep eutectic solvents from choline chloride and betaine – physicochemical properties. J. Mol. Liq. 241, 654–661. https://doi.org/10.1016/j.molliq.2017.06.051.

Bai, L., Chen, H., Wang, W., Ma, X., Sun, Z., Zhang, J., Yuan, Z., Wei, D., Yang, H., Niu, Y., 2018. A Method of Extraction Fruits and Vegetables Residue Prepares Levelling Agent. CN108611897A. https://patents.google.com/patent/CN108611897A/en?oq=CN108611897A. (Accessed 15 October 2021).

Benoit, C., Virginie, C., Boris, V., 2021. The Use of NADES to Support Innovation in the Cosmetic Industry, first ed. Elsevier Ltd. https://doi.org/10.1016/bs.abr.2020.09.009

Cao, J., Su, E., 2021. Hydrophobic deep eutectic solvents : the new generation of green solvents for diversified and colorful applications in green chemistry. J. Clean. Prod. 314, 127965 https://doi.org/10.1016/j.jclepro.2021.127965.

Cao, F., Su, E., Cao, J., Wang, G., Zhao, L., 2017. It Is a Kind of to Be Used to Extract Deep Congruent Melting Solvent of Five Kinds of Organic Acids of Ginkgo Leaf and Preparation Method Thereof and Extracting Method Simultaneously. CN107694147A. https://patents.google.com/patent/CN107694147A/en?oq=CN107694147A. (Accessed 15 October 2021).

Cao, J., Chen, L., Li, M., Cao, F., Zhao, L., Su, E., 2018. Two-phase systems developed with hydrophilic and hydrophobic deep eutectic solvents for simultaneously extracting various bioactive compounds with different polarities. Green Chem. 20, 1879–1886. https://doi.org/10.1039/c7gc03820h.

Caprin, B., Charton, V., Demarne, F., 2015. Vegetable Extracts for Cosmetics, Solvents and Methods for Obtaining Them. FR3036618B1. https://patents.google.com/patent/FR3036618B1/en?oq=FR3036618B1. (Accessed 15 October 2021).

Charton, V., Caprin, B., Bechetoille, N., 2019. Aesculus Hippocastanum Extract. US10363212B2. https://patents.google.com/patent/US10363212B2/en?oq=US10363212B2. (Accessed 15 October 2021).

Chemat, F., Abert-vian, M., Fabiano-tixier, A.S., Strube, J., Uhlenbrock, L., Gunjevic, V., Cravotto, G., 2019. Green extraction of natural products . Origins , current status , and future challenges. Trends Anal. Chem. 118, 248–263. https://doi.org/10.1016/j.trac.2019.05.037.

Chen, Y., Dang, J., Yan, X., Huang, Y., Li, D., Lu, F., 2020. Deep Eutectic Solvent and Method for Extracting Flavone Di-C-glycoside from Premna Fulva. CN111171095A.

https://patents.google.com/patent/CN111171095A/en?oq=CN111171095A. (Accessed 15 October 2021).
Chen, B., Peng, Z., Li, C., Feng, Y., Sun, Y., Tang, X., 2021. Catalytic Conversion of Biomass to Furanic Derivatives with Deep Eutectic Solvents, vol. 361102, pp. 1496–1506. https://doi.org/10.1002/cssc.202100001.
Dai, J., Mumper, R.J., 2010. Plant Phenolics: Extraction, Analysis and Their Antioxidant and Anticancer Properties, Molecules, pp. 7313–7352. https://doi.org/10.3390/molecules15107313.
Dai, Y., van Spronsen, J., Witkamp, G.J., Verpoorte, R., Choi, Y.H., 2013a. Natural deep eutectic solvents as new potential media for green technology. Anal. Chim. Acta 766, 61–68. https://doi.org/10.1016/j.aca.2012.12.019.
Dai, Y., Witkamp, G.J., Verpoorte, R., Choi, Y.H., 2013b. Natural deep eutectic solvents as a new extraction media for phenolic metabolites in carthamus tinctorius L. Anal. Chem. 85, 6272–6278. https://doi.org/10.1021/ac400432p.
Dai, Y., Witkamp, G.J., Verpoorte, R., Choi, Y.H., 2015. Tailoring properties of natural deep eutectic solvents with water to facilitate their applications. Food Chem. 187, 14–19. https://doi.org/10.1016/j.foodchem.2015.03.123.
Donato, M.T., Colaço, R., Branco, L.C., Saramago, B., 2021. A review on alternative lubricants : ionic liquids as additives and deep eutectic solvents. J. Mol. Liq. 333, 116004 https://doi.org/10.1016/j.molliq.2021.116004.
Durand, E., Lecomte, J., Upasani, R., Chabi, B., Bayrasy, C., Baréa, B., Jublanc, E., Clarke, M.J., Moore, D.J., Crowther, J., Wrutniak-cabello, C., Villeneuve, P., 2017. Evaluation of the ROS Inhibiting Activity and Mitochondrial Targeting of Phenolic Compounds in Fibroblast Cells Model System and Enhancement of Eff Iciency by Natural Deep Eutectic Solvent (NADES) Formulation. https://doi.org/10.1007/s11095-017-2124-4.
Enrica, M., Pietro, D., Mele, A., 2021. Deep eutectics and analogues as electrolytes in batteries. J. Mol. Liq. 338, 116597 https://doi.org/10.1016/j.molliq.2021.116597.
European Commission, 2009. Regulation (EC) No 1223/2009 of the European parliament and of the Council of 30 november 2009 on cosmetic products. Off. J. Eur. Union 342–359. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02009R1223-20201203. (Accessed 10 December 2021).
Gao, J., Zhou, X., Li, W., Zhang, L., 2019. A Kind of Method that Depth Eutectic Solvent Microemulsion Extracts System and Extracts Astaxanthin. CN110317156A. https://patents.google.com/patent/CN110317156A/en?oq=CN110317156A. (Accessed 15 October 2021).
García, A., Rodríguez-Juan, E., Rodríguez-Gutiérrez, G., Rios, J.J., Fernández-Bolaños, J., 2016. Extraction of phenolic compounds from virgin olive oil by deep eutectic solvents (DESs). Food Chem. 197, 554–561. https://doi.org/10.1016/j.foodchem.2015.10.131.
Grillo, G., Gunjević, V., Radošević, K., Redovniković, I.R., Cravotto, G., 2020. Deep eutectic solvents and nonconventional technologies for blueberry-peel extraction: kinetics, anthocyanin stability, and antiproliferative activity. Antioxidants 9, 1–28. https://doi.org/10.3390/antiox9111069.
Hong, M., Tao, Z., 2020. Method for Extracting Carotenoid by Natural Deep Eutectic Solvent. CN111116443A. https://patents.google.com/patent/CN111116443A/en?oq=CN111116443A. (Accessed 15 October 2021).
Ivanović, M., Alañón, M.E., Arráez-Román, D., Segura-Carretero, A., 2018. Enhanced and green extraction of bioactive compounds from Lippia citriodora by tailor-made natural deep eutectic solvents. Food Res. Int. 111, 67–76. https://doi.org/10.1016/j.foodres.2018.05.014.
Jeong, K.M., Lee, M.S., Nam, M.W., Zhao, J., Jin, Y., Lee, D.K., Kwon, S.W., Jeong, J.H., Lee, J., 2015. Tailoring and recycling of deep eutectic solvents as sustainable and efficient extraction media. J. Chromatogr. A 1424, 10–17. https://doi.org/10.1016/j.chroma.2015.10.083.
Jeong, K.M., Ko, J., Zhao, J., Jin, Y., Yoo, D.E., Han, S.Y., Lee, J., 2017. Multi-functioning deep eutectic solvents as extraction and storage media for bioactive natural products that are readily applicable to cosmetic products. J. Clean. Prod. 151, 87–95. https://doi.org/10.1016/j.jclepro.2017.03.038.
Kalyniukova, A., Holuša, J., Musiolek, D., Sedlakova-Kadukova, J., Płotka-Wasylka, J., Andruch, V., 2021. Application of deep eutectic solvents for separation and determination of bioactive compounds in medicinal plants. Ind. Crop. Prod. 172 https://doi.org/10.1016/j.indcrop.2021.114047.
Kumar, A.K., Sharma, S., Dixit, G., Shah, E., Patel, A., Boczkaj, G., 2020. Techno-economic evaluation of a natural deep eutectic solvent-based biorefinery: exploring different design scenarios. Biofuels, Bioproducts and Biorefining 14, 746–763. https://doi.org/10.1002/bbb.2110.
Lavaud, A., Laguerre, M., Birtic, S., Fabiano Tixier, A.S., Roller, M., Chemat, F., Bily, A. C., 2015. Eutectic Extraction Solvents, Extraction Methods by Eutectigenesis Using Said Solvents, and Extracts Derived from Said Extraction Methods. WO2016162703A1. https://patents.google.com/patent/WO2016162703A1/en?oq=WO2016162703+A1. (Accessed 15 October 2021).
Li, C., Yao, Z., Yin, J., Cui, Y., Wang, A., Jia, Y., 2013. Deep-eutectic-solvent Based Supported Liquid Membrane as Well as Preparation Method and Application Thereof. CN103357278A. https://patents.google.com/patent/CN103357278A/en?oq=CN103357278A. (Accessed 15 October 2021).
Li, K., Gong, X., Chen, S., 2017. A Kind of Method Using 5 Kinds of Macamides in Deep Co-melting Solvent Extraction Measure Maca. CN107748211A. https://patents.google.com/patent/CN107748211A/en?oq=CN107748211A. (Accessed 15 October 2021).
Liu, Y., Friesen, J.B., McAlpine, J.B., Lankin, D.C., Chen, S.N., Pauli, G.F., 2018. Natural deep eutectic solvents: properties, applications, and perspectives. J. Nat. Prod. 81, 679–690. https://doi.org/10.1021/acs.jnatprod.7b00945.
López, R., D'Amato, R., Trabalza-Marinucci, M., Regni, L., Proetti, P., Maratta, A., Cerutti, S., Pacheco, P., 2020. Green and simple extraction of free seleno-amino acids from powdered and lyophilized milk samples with natural deep eutectic solvents. Food Chem. 326, 126965 https://doi.org/10.1016/j.foodchem.2020.126965.
Lou, W., Yang, F., Zong, M., Hua, Y., Liang, J., 2016a. Method for Extracting Anthocyanin by Using Deep Eutectic Solvent. CN105777696B. https://patents.google.com/patent/CN105777696B/en?oq=CN105777696B. (Accessed 15 October 2021).
Lou, W., Zhao, B., Zong, M., Chen, Q., Hua, Y., Yang, J., 2016b. Method for Extracting Rutin from sophora Japonica on Basis of Deep Eutectic Solvents. DESs). CN106046082A. https://patents.google.com/patent/CN106046082A/en?oq=CN106046082A. (Accessed 15 October 2021).
Malolan, R., Panchamoorthy, K., Dai, G., Vo, V.N., Sai, R., 2021. Green ionic liquids and deep eutectic solvents for desulphurization , denitrification , biomass , biodiesel , bioethanol and hydrogen fuels : a review. Environ. Chem. Lett. 19, 1001–1023. https://doi.org/10.1007/s10311-020-01113-7.
Mansur, A.R., Song, N.E., Jang, H.W., Lim, T.G., Yoo, M., Nam, T.G., 2019. Optimizing the ultrasound-assisted deep eutectic solvent extraction of flavonoids in common buckwheat sprouts. Food Chem. 293, 438–445. https://doi.org/10.1016/j.foodchem.2019.05.003.
Mbous, Y.P., Hayyan, M., Wong, W.F., Looi, C.Y., Hashim, M.A., 2017. Unraveling the cytotoxicity and metabolic pathways of binary natural deep eutectic solvent systems. Sci. Rep. 7, 41257 https://doi.org/10.1038/srep41257.
Milani, G., Vian, M., Cavalluzzi, M.M., Franchini, C., Corbo, F., Lentini, G., Chemat, F., 2020. Ultrasound and deep eutectic solvents: an efficient combination to tune the mechanism of steviol glycosides extraction. Ultrason. Sonochem. 69 https://doi.org/10.1016/j.ultsonch.2020.105255.
Mitar, A., Panić, M., Prlić Kardum, J., Halambek, J., Sander, A., Zagajski Kučan, K., Radojčić Redovniković, I., Radošević, K., 2019. Physicochemical properties, cytotoxicity, and antioxidative activity of natural deep eutectic solvents containing organic acid. Chem. Biochem. Eng. Q. 33, 1–18. https://doi.org/10.15255/CABEQ.2018.1454.
Nam, M.W., Zhao, J., Lee, M.S., Jeong, J.H., Lee, J., 2015. Enhanced extraction of bioactive natural products using tailor-made deep eutectic solvents: application to flavonoid extraction from Flos sophorae. Green Chem. 17, 1718–1727. https://doi.org/10.1039/c4gc01556h.
Ochoa, S., Durango-Zuleta, M.M., Felipe Osorio-Tobón, J., 2020. Techno-economic evaluation of the extraction of anthocyanins from purple yam (Dioscorea alata) using ultrasound-assisted extraction and conventional extraction processes. Food Bioprod. Process. 122, 111–123. https://doi.org/10.1016/j.fbp.2020.04.007.
Paiva, A., Craveiro, R., Aroso, I., Martins, M., Reis, R.L., Duarte, A.R.C., 2014. Natural deep eutectic solvents - solvents for the 21st century. ACS Sustain. Chem. Eng. 2, 1063–1071. https://doi.org/10.1021/sc500096j.
Panić, M., Majerić Elenkov, M., Roje, M., Cvjetko Bubalo, M., Radojčić Redovniković, I., 2017. Plant-mediated stereoselective biotransformations in natural deep eutectic solvents. Process Biochem. https://doi.org/10.1016/j.procbio.2017.12.010.
Panić, M., Gunjević, V., Cravotto, G., Radojčić Redovniković, I., 2019a. Enabling technologies for the extraction of grape-pomace anthocyanins using natural deep eutectic solvents in up-to-half-litre batches extraction of grape-pomace anthocyanins using NADES. Food Chem. 300 https://doi.org/10.1016/j.foodchem.2019.125185.
Panić, M., Stojković, M.R., Kraljić, K., Škevin, D., 2019b. Ready-to-use green polyphenolic extracts from food by-products. Food Chem. 283, 628–636. https://doi.org/10.1016/j.foodchem.2019.01.061.
Panić, M., Gunjević, V., Cravotto, G., Radojčić Redovniković, I., 2019c. Enabling technologies for the extraction of grape-pomace anthocyanins using natural deep eutectic solvents in up-to-half-litre batches extraction of grape-pomace anthocyanins using NADES. Food Chem. 300 https://doi.org/10.1016/j.foodchem.2019.125185.
Panić, M., Cvjetko Bubalo, M., Radojčić Redovniković, I., 2020. Designing a biocatalytic process involving deep eutectic solvents. J. Chem. Technol. Biotechnol. https://doi.org/10.1002/jctb.6545.
Paul, Y., Hayyan, M., Hayyan, A., Fen, W., Ali, M., Yeng, C., 2017. Applications of deep eutectic solvents in biotechnology and bioengineering — promises and challenges. Biotechnol. Adv. 35, 105–134. https://doi.org/10.1016/j.biotechadv.2016.11.006.
Pena-Pereira, F., Namieśnik, J., 2014. Ionic liquids and deep eutectic mixtures: sustainable solvents for extraction processes. ChemSusChem 7, 1784–1800. https://doi.org/10.1002/cssc.201301192.
Petcavich, R., 2013. Method for Separating Hydrocarbons from Oil-Containing Rock by Using Deep Eutectic Solvent. CN104130798A. https://patents.google.com/patent/CN104130798A/en?oq=CN104130798A. (Accessed 15 October 2021).
Peters, C.J., Kroon, M., Warrag, S., Reinalda, D., 2017. Mercury Capture from Hydrocarbon Fluids Using Deep Eutectic Solvents. WO2019106406A1. https://patents.google.com/patent/WO2019106406A1/en?oq=WO2019106406A1. (Accessed 15 October 2021).
Płotka-Wasylka, J., Wojnowski, W., 2021. Complementary green analytical procedure index (ComplexGAPI) and software. Green Chem. 23, 8657–8665. https://doi.org/10.1039/d1gc02318g.
12 principles of green chemistry - American chemical society, (n.d.). https://www.acs.org/content/acs/en/greenchemistry/principles/12-principles-of-green-chemistry.html (accessed October 14, 2021).
Qin, H., Hu, X., Wang, J., Cheng, H., Chen, L., Qi, Z., 2020. Overview of acidic deep eutectic solvents on synthesis, properties and applications. Green Energy. Environ. 5, 8–21. https://doi.org/10.1016/j.gee.2019.03.002.
Radošević, K., Cvjetko Bubalo, M., Gaurina Srček, V., Grgas, D., Landeka Dragičević, T., Redovniković, R.I., 2015a. Evaluation of toxicity and biodegradability of choline chloride based deep eutectic solvents. Ecotoxicol. Environ. Saf. 112, 46–53. https://doi.org/10.1016/j.ecoenv.2014.09.034.
Radošević, K., Cvjetko Bubalo, M., Gaurina Srček, V., Grgas, D., Landeka Dragičević, T., Redovniković, R.I., 2015b. Evaluation of toxicity and biodegradability of choline

chloride based deep eutectic solvents. Ecotoxicol. Environ. Saf. 112, 46–53. https://doi.org/10.1016/j.ecoenv.2014.09.034.

Radošević, K., Železnjak, J., Cvjetko Bubalo, M., Radojčić Redovniković, I., Slivac, I., Gaurina Srček, V., 2016. Comparative in vitro study of cholinium-based ionic liquids and deep eutectic solvents toward fish cell line. Ecotoxicol. Environ. Saf. 131, 30–36. https://doi.org/10.1016/j.ecoenv.2016.05.005.

Radošević, K., Čanak, I., Panić, M., Markov, K., Bubalo, M.C.M.C., Frece, J., Srček, V.G.V.G., Redovniković, I.R.I.R., 2018. Antimicrobial, cytotoxic and antioxidative evaluation of natural deep eutectic solvents. Environ. Sci. Pollut. Control Ser. 25, 14188–14196. https://doi.org/10.1007/s11356-018-1669-z.

Rao, G., 2019. Deep Eutectic Solvent for Extracting Flavone in Phellinus Igniarius, Preparation Method Thereof and Extraction Method of Flavone in Phellinus Igniarius. CN110721206A. https://patents.google.com/patent/CN110721206A/en?oq=CN110721206A. (Accessed 15 October 2021).

Rente, D., Paiva, A., Duarte, A.R., 2021. The role of hydrogen bond donor on the extraction of phenolic compounds from natural matrices using deep eutectic systems. Molecules 26. https://doi.org/10.3390/molecules26082336.

Rublova, Y.D., Kityk, A.A., Bannyk, N.G., Protsenko, V.S., Danilov, F.I., 2019. The influence of various factors on corrosion of mild steel in deep eutectic solvents. Mater. Today Proc. 6, 232–236. https://doi.org/10.1016/j.matpr.2018.10.099.

Ruesgas-Ramón, M., Figueroa-Espinoza, M.C., Durand, E., 2017. Application of deep eutectic solvents (DES) for phenolic compounds extraction: overview, challenges, and opportunities. J. Agric. Food Chem. 65, 3591–3601. https://doi.org/10.1021/acs.jafc.7b01054.

Smith, E.L., Abbott, A.P., Ryder, K.S., 2014. Deep eutectic solvents (DESs) and their applications. Chem. Rev. 114, 11060–11082. https://doi.org/10.1021/cr300162p.

Su, E., Cao, J., Cao, F., Li, M., Mei, N., Wang, G., Duan, X., 2017a. A Kind of Extraction Blue and White Plain Deep Congruent Melting Solvent of Ginkgo Phyllogen and Preparation Method Thereof and Extracting Method. CN107759556A. https://patents.google.com/patent/CN107759556A/en?oq=CN107759556A. (Accessed 15 October 2021).

Su, E., Cao, J., Li, M., Cao, F., Chen, L., Zhao, L., Wang, Y., 2017b. A Kind of Two-phase Depth Congruent Melting Solvent for Extracting Active Components of Ginkgo Leaves and Preparation Method Thereof and Extracting Method. CN107789376A. https://patents.google.com/patent/CN107789376A/en?oq=CN107789376A. (Accessed 15 October 2021).

Svigelj, R., Dossi, N., Grazioli, C., Toniolo, R., 2021. Deep Eutectic Solvents (DESs) and Their Application in Biosensor Development.

Tan, J., Shang, X., Zhang, Z., Dou, Y., Liu, X., Du, Y., Li, R., 2018a. Deep Eutectic Solvent and Method for Extracting Isoflavones from Chickpeas by Using Deep Eutectic Solvent. CN110698526A. https://patents.google.com/patent/CN110698526A/en?oq=CN110698526A. (Accessed 15 October 2021).

Tan, J., Shang, X., Zhang, Z., Dou, Y., Liu, X., Du, Y., Li, R., 2018b. Deep Eutectic Solvent and Method for Extracting Flavonoid Compounds from Cyclocarya Paliurus Leaves by Using Deep Eutectic Solvent. CN110693939A. https://patents.google.com/patent/CN110693939A/en?oq=CN110693939A. (Accessed 15 October 2021).

Tan, Z., Wang, C., Cai, C., Yi, Y., Zeng, L., Wang, H., Yang, Y., Li, M., 2020. Temperature Response Type Eutectic Solvent and Extraction Method of Ganoderma Lucidum Polysaccharide. CN111269328A. https://patents.google.com/patent/CN111269328A/en?oq=CN111269328A. (Accessed 15 October 2021).

Torregrosa-Crespo, J., Marset, X., Guillena, G., Ramón, D.J., María Martínez-Espinosa, R., 2020. New guidelines for testing "Deep eutectic solvents" toxicity and their effects on the environment and living beings. Sci. Total Environ. 704, 135382 https://doi.org/10.1016/j.scitotenv.2019.135382.

Tran, M.K., Rodrigues, M.-T.F., Babu, G., Gullapalli, H., Ajayan, P.M., 2020. Recycling Li-Ion Batteries Using Green Chemicals and Processes. US20200399737A1. https://patents.google.com/patent/US20200399737A1/en?oq=US2020399737A1. (Accessed 15 October 2021).

van Spronsen, J., Witkamp, G.-J., Hollman, F., Choi, Y.H., Verpoorte, R., 2011. Process for Extracting Materials from Biological Material. US9441146B2. https://patents.google.com/patent/US9441146B2/en. (Accessed 15 October 2021).

Vilkhu, K., Mawson, R., Simons, L., Bates, D., 2008. Applications and opportunities for ultrasound assisted extraction in the food industry - a review. Innovat. Food Sci. Emerg. Technol. 9, 161–169. https://doi.org/10.1016/j.ifset.2007.04.014.

Viviane, C., Martins, B., Oliveira, L., Rosemeire, F., De Lucca, S., 2019. Polyphenols as Natural Antioxidants in Cosmetics Applications, Jornal of Cosmetic Dermatology, pp. 1–5. https://doi.org/10.1111/jocd.13093.

Wikene, K.O., Rukke, H.V., Bruzell, E., Tønnesen, H.H., 2017. Investigation of the antimicrobial effect of natural deep eutectic solvents (NADES) as solvents in antimicrobial photodynamic therapy. J. Photochem. Photobiol., B 171, 27–33. https://doi.org/10.1016/j.jphotobiol.2017.04.030.

Wils, L., Hilali, S., Boudesocque-delaye, L., 2021. Biomass Valorization Using Natural Deep Eutectic Solvents : what ' S New in France ?.

Wojeicchowski, J.P., Ferreira, A.M., Abranches, D.O., Mafra, M.R., Coutinho, J.A.P., 2020. Using COSMO-RS in the design of deep eutectic solvents for the extraction of antioxidants from rosemary. ACS Sustain. Chem. Eng. 8, 12132–12141. https://doi.org/10.1021/acssuschemeng.0c03553.

Xu, M., Ran, L., Chen, N., Fan, X., Ren, D., Yi, L., 2019. Polarity-dependent extraction of fl avonoids from citrus peel waste using a tailor-made deep eutectic solvent. Food Chem. 297, 124970 https://doi.org/10.1016/j.foodchem.2019.124970.

Yang, G., Qi, L., Liu, J., Chen, J., 2020. Method for Separating and Extracting Lignin by In-Situ Synthesis of Deep Eutectic Solvent - Google Patents. CN112029115A. https://patents.google.com/patent/CN112029115A/en?oq=CN112029115A. (Accessed 15 October 2021).

Yu, L., Huo, H., Di, Jianjun, Tian, X., Wang, H., Xu, Y., Li, X., Zhou, W., 2020. Method for Green and Efficient Extraction of Red Clover Isoflavone by Using Natural Deep Eutectic Solvent. CN112125894A. https://patents.google.com/patent/CN112125894A/en?oq=CN112125894A. (Accessed 15 October 2021).

Zainal-abidin, M.H., Hayyan, M., Hayyan, A., 2017. New horizons in the extraction of bioactive compounds using deep eutectic solvents : a review. Anal. Chim. Acta 979, 1–23. https://doi.org/10.1016/j.aca.2017.05.012.

Zhang, Q., De Oliveira Vigier, K., Royer, S., Jérôme, F., 2012. Deep eutectic solvents: syntheses, properties and applications. Chem. Soc. Rev. 41, 7108–7146. https://doi.org/10.1039/c2cs35178a.