

# The Most Potent Natural Pharmaceuticals, Cosmetics, and Food Ingredients Isolated from Plants with Deep Eutectic Solvents

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**ABSTRACT:** There is growing interest in reducing the number of synthetic products or additives and replacing them with natural ones. The pharmaceutical, cosmetic, and food industries are especially focused on natural and bioactive chemicals isolated from plants or microorganisms. The main challenge here is to develop efficient and ecological methods for their isolation. According to the strategies and rules of sustainable development and green chemistry, green solvents and environmentally friendly technologies must be used. The application of deep eutectic solvents as efficient and biodegradable solvents seems to be a promising alternative to traditional methods. They are classified as being green and ecological but, most importantly, very efficient extraction media compared to organic solvents. The aim of this review is to present the recent findings on green extraction, as well as the biological activities and the possible applications of natural plant ingredients, namely, phenolics, flavonoids, terpenes, saponins, and some others. This paper thoroughly reviews modern, ecological, and efficient extraction methods with the use of deep eutectic solvents (DESs). The newest findings, as well as the factors influencing the efficiency of extraction, such as water content, and hydrogen bond donor and acceptor types, as well as the extraction systems, are also discussed. New solutions to the major problem of separating DESs from the extract and for solvent recycling are also presented.

**KEYWORDS:** *bioactive compounds from plants, bioactive ingredients in cosmetics, natural pharmaceuticals, natural food additives, deep eutectic solvents, green solvents*

## 1. INTRODUCTION

Nowadays, reducing global pollution and introducing sustainable development in all areas of life should be everyone's priority. A sustainable development strategy to save the planet and the environment consists of many goals, and one of the most important is responsible production and consumption. A growing amount of interest and demand for natural components with promising properties such as antiaging, anti-inflammatory, anticancer, and antimicrobial has been observed in the pharmaceutical, cosmetic, and food industries. The most interesting groups of valuable, plant-originated compounds include phenolics, flavonoids, terpenoids, and saponins. The major concern involves efficient and ecological isolation of these compounds from natural sources. The technologies applied should meet the requirements of green chemistry, which means that the use of many organic solvents is restricted. There are still many attempts to find green, efficient, and inexpensive methods for the isolation of natural plant ingredients, both hydrophilic and hydrophobic. The new trend, widely explored in many fields of industry, is to apply deep eutectic solvents (DESs), composed of naturally occurring ingredients. These have been proven to be efficient, biodegradable, and environmentally friendly media, useful in many branches of industry (Figure 1).<sup>1–16</sup>

DESs were first introduced in 2003 by Abbott et al., and since then, huge development and interest in these solvents have been observed.<sup>17</sup> They have been considered as potential replacements for ionic liquids (ILs), after aspects of the

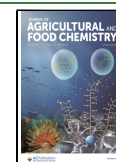
possible toxicity of some ILs to living organisms have emerged. Initially, the research focused mostly on hydrophilic DESs, and the first information on hydrophobic ones appeared in 2015. The structures of the most popular DESs are based on noncovalent interactions. Depending on the character of the hydrogen bond acceptor (HBA) and the hydrogen bond donor (HBD), interactions such as hydrogen bonding, van der Waals interactions, or  $\pi$ – $\pi$  stacking occur. Recently, novel eutectic systems, namely, eutectic molecular liquids (EMLs), were defined, and several other noncovalent interactions were identified, including not only hydrogen bonding and  $\pi$ – $\pi$  stacking but also  $\sigma$ -hole (halogen, pnictogen, and tetrel bonds),  $\pi$ -hole,  $\kappa$ -hole, and  $\mu$ -hole bonding interactions.<sup>18,19</sup> There is a huge interest in composing DESs with new and interesting properties as well as in explaining the structure–activity relationship and the interactions occurring between different HBAs and HBDs.<sup>20–22</sup> The most valuable feature of DESs seems to be the possibility of obtaining almost unlimited numbers of tailor-made solvents by selecting appropriate HBDs and HBAs. Additionally, many DESs (also named natural deep eutectic solvents, NADESs) are bioderived, green,

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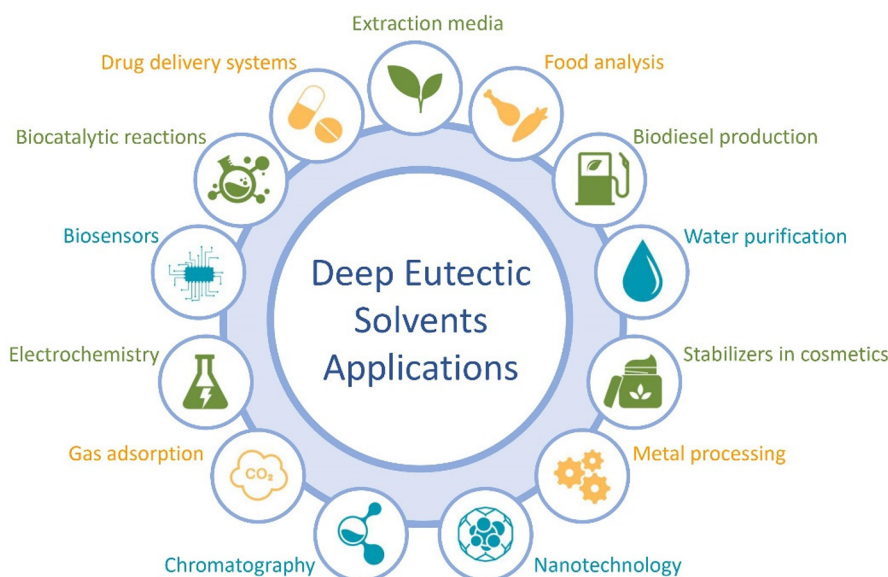


Figure 1. Wide range of DES applications.<sup>4–16</sup>

biocompatible, biodegradable, and nontoxic chemicals, unlike classic solvents (including solvents belonging to volatile organic compounds, VOCs) or some ILs. However, there are a few negative aspects for DES applications. First is the high viscosity of many DESs. Also, due to the high hygroscopicity of some DESs (especially those with choline chloride), they can absorb moisture from the air, which may cause problems with handling and storage. Additionally, even though the majority of DESs are considered thermostable, some can decompose at high temperatures and some can be corrosive.<sup>23</sup> The major challenge in using DESs as extraction media is to efficiently separate them from the extract and to recycle them for reuse. The main advantages and disadvantages of DESs as extraction media are presented in Figure 2. It is clear that the advantages far outweigh the disadvantages, so DESs are much better and more preferable substitutes for organic solvents.

Many papers discussing the extractions of plant ingredients with DESs have been published in recent times. These focus on several important aspects of efficient extraction, including the types and properties of the solvents, the time of extraction, and the water content and temperature.<sup>24,25</sup> Different

extraction techniques, e.g., microwave- and ultrasound-assisted extraction and microextraction, have been reviewed.<sup>26–28</sup> The analytical methods applied to the characteristics of the extracted substances, as well as the problems with the viscosity and recovery of the extracted compounds, are also widely discussed.<sup>29,30</sup> Special attention is paid to the extraction of phenolic compounds, flavonoids, proteins, biopolymers, and carbohydrates from waste biomass or algae.<sup>24,31,32</sup> Among all of the types of DESs used in modern extraction, the potential for hydrophobic DESs was underlined in many recent papers, and thoroughly reviewed by Sportiello et al.<sup>33</sup> These DESs can be characterized by the presence of compounds with long alkyl chain or cycloalkyl groups. They are composed of, e.g., lauric acid, decanoic acid, thymol, menthol, tetraheptylammonium chloride, or tetraoctylammonium chloride as HBAs and long chain carboxylic acids, levulinic acid, lidocaine, or camphor as HBDs. Efficient extraction of food contaminants, chelating properties, and also extraction of bioactive compounds such as artemisinin, carotenoids, or tocopherols are widely reported.<sup>33</sup> The importance of the extraction of natural substances with DESs is also confirmed by the number of patent applications filed in recent years. According to the Espacenet database, in only 2022–2023, out of 91 documents claiming extractions using DESs, ~67 patent applications were filed for the extraction of natural compounds (<https://worldwide.espacenet.com/>; query: deep eutectic solvent AND extraction; selected by earliest publication date; accessed 2023-10-05). The newest inventions, apart from the classic DESs, focus on extractions with NADESs, hydrophobic DESs, binary solvents (e.g., composed of ILs and DESs), or deep eutectic solvent microemulsion extraction systems, as well as the use of ultrasound- or microwave-assisted processes.

This review provides a compilation of the newest information on the significance of the most important groups of bioactive compounds from plants, namely, phenolics, flavonoids, terpenes, saponins, polysaccharides, and some others. It focuses on the novel findings of their biological activities, the new potential applications of the extracted chemicals, and ecologically sound and efficient extraction methods with the use of DESs. The advantage of applying

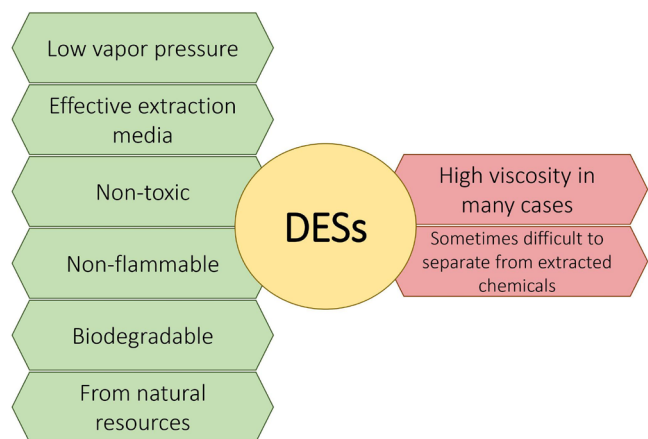


Figure 2. Advantages (green) and disadvantages (red) of deep eutectic solvents applied as extraction media.

Table 1. Chemical Structures, Properties, and Application of Phenolic Compounds Present in Plants

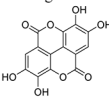
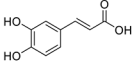
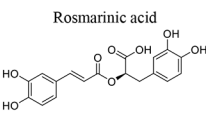
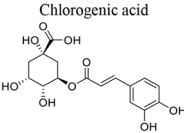
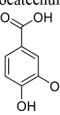
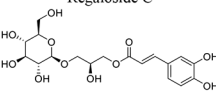
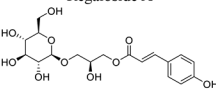
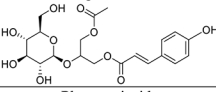
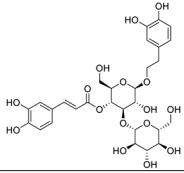
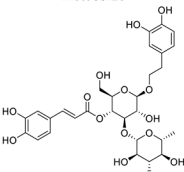
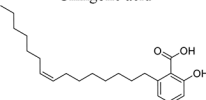
| Name and chemical structure                                                                                      | CAS number  | Activity                                                                                                                                                                                                          | Applications/potential applications                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                      |                                                                                                                                                                                                                                                       |
|------------------------------------------------------------------------------------------------------------------|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                  |             |                                                                                                                                                                                                                   | Pharmaceuticals industry                                                                                                                                                                                                                                                                                                                                                            | Cosmetics industry                                                                                                                                                                                   | Food industry                                                                                                                                                                                                                                         |
| <b>Gallic acid</b><br>          | 149-91-7    | <ul style="list-style-type: none"> <li>- Antioxidative</li> <li>- Anti-inflammatory</li> <li>- Induces apoptosis</li> </ul>                                                                                       | <ul style="list-style-type: none"> <li>- Diabetes treatment<sup>41</sup></li> <li>- Colon, lung, oral cancer prevention<sup>42,44</sup></li> <li>- Regeneration of endogenous defense system<sup>45</sup></li> </ul>                                                                                                                                                                | <ul style="list-style-type: none"> <li>- Reduces skin redness (in the form of diglucosyl)<sup>47</sup></li> </ul>                                                                                    | <ul style="list-style-type: none"> <li>- Lowers the solubility of gelatin packaging film and enhances its thermal stability<sup>43</sup></li> <li>- Food packaging additive that changes color according to product freshness<sup>46</sup></li> </ul> |
| <b>Ellagic acid</b><br>         | 476-66-4    | <ul style="list-style-type: none"> <li>- Antioxidative</li> <li>- Neuroprotective</li> </ul>                                                                                                                      | <ul style="list-style-type: none"> <li>- Adjuvant in chemotherapy and radiotherapy; increases tumor sensitivity<sup>48</sup></li> <li>- Cancer treatment<sup>49</sup></li> <li>- Dementia treatment<sup>50</sup></li> </ul>                                                                                                                                                         | <ul style="list-style-type: none"> <li>- Wound treatment and protection<sup>51</sup></li> </ul>                                                                                                      | -                                                                                                                                                                                                                                                     |
| <b>Caffeic acid</b><br>         | 501-16-6    | <ul style="list-style-type: none"> <li>- Anti-inflammatory</li> <li>- Neuroprotective</li> <li>- Antimicrobial</li> </ul>                                                                                         | <ul style="list-style-type: none"> <li>- Stimulates the biosynthesis of synaptic proteins—Alzheimer's disease treatment<sup>52</sup></li> <li>- Inhibits cancer cells migration<sup>53</sup></li> <li>- Antimicrobial drugs<sup>54</sup></li> <li>- Hyperglycemia treatment<sup>55</sup></li> </ul>                                                                                 | <ul style="list-style-type: none"> <li>- Provides antioxidant activity to chitosan–collagen hydrogels<sup>56</sup></li> </ul>                                                                        | <ul style="list-style-type: none"> <li>- Increases the resistance of chitosan packaging film to microbial contamination and moisture migration<sup>57</sup></li> </ul>                                                                                |
| <b>Rosmarinic acid</b><br>      | 20283-92-5  | <ul style="list-style-type: none"> <li>- Anti-inflammatory</li> <li>- Antioxidative</li> <li>- Neuroprotective</li> </ul>                                                                                         | <ul style="list-style-type: none"> <li>- Promotes metal chelation, which protects the neurological system<sup>58</sup></li> </ul>                                                                                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>- Protects DNA from UV radiation<sup>59</sup></li> <li>- Protects fibroblasts from parabens present in cosmetics<sup>60</sup></li> </ul>                      | <ul style="list-style-type: none"> <li>- Prevents oxidation of omega-3 acids<sup>61</sup></li> </ul>                                                                                                                                                  |
| <b>Chlorogenic acid</b><br>     | 202650-88-2 | <ul style="list-style-type: none"> <li>- Antioxidative</li> </ul>                                                                                                                                                 | <ul style="list-style-type: none"> <li>- Decreases cancer cell viability and growth<sup>62,63</sup></li> </ul>                                                                                                                                                                                                                                                                      | <ul style="list-style-type: none"> <li>- Protects cells from UVA radiation, slows down collagen degradation<sup>64</sup></li> <li>- Promotes regeneration of dermal proteins<sup>65</sup></li> </ul> | <ul style="list-style-type: none"> <li>- Lowers allergenicity and increases thermal stability of wheat gluten hydrolysate<sup>66</sup></li> </ul>                                                                                                     |
| <b>Protocatechuic acid</b><br> | 99-50-3     | <ul style="list-style-type: none"> <li>- Antioxidative</li> <li>- Anti-inflammatory</li> <li>- Induces apoptosis</li> </ul>                                                                                       | <ul style="list-style-type: none"> <li>- Reduces cancer cell viability by inducing apoptosis<sup>67</sup></li> <li>- Reduces neurodegeneration<sup>68</sup></li> <li>- Prevents diabetic complications, reduces blood glucose levels<sup>69</sup></li> </ul>                                                                                                                        | <ul style="list-style-type: none"> <li>- Enhances collagen synthesis<sup>70</sup></li> </ul>                                                                                                         | <ul style="list-style-type: none"> <li>- Increases barrier properties of gelatin films<sup>71</sup></li> <li>- Has antibacterial activity against pathogens present in food<sup>72</sup></li> </ul>                                                   |
| <b>Regaloside C</b><br>       | 117591-85-2 |                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                      |                                                                                                                                                                                                                                                       |
| <b>Regaloside A</b><br>       | 114420-66-5 | <ul style="list-style-type: none"> <li>- Anti-inflammatory</li> <li>- Antioxidative</li> </ul>                                                                                                                    | <ul style="list-style-type: none"> <li>- Strong anti-inflammatory activity against inflammatory factors, e.g., inhibition of COX-2 expression<sup>73</sup></li> </ul>                                                                                                                                                                                                               | -                                                                                                                                                                                                    | -                                                                                                                                                                                                                                                     |
| <b>Regaloside B</b><br>       | 114420-67-6 |                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                      |                                                                                                                                                                                                                                                       |
| <b>Plantamajoside</b><br>     | 104777-68-6 | <ul style="list-style-type: none"> <li>- Antioxidative</li> <li>- Anti-inflammatory</li> <li>- Induces apoptosis</li> <li>- Inhibits proliferation</li> <li>- Neuroprotective</li> </ul>                          | <ul style="list-style-type: none"> <li>- Inhibits hepatocellular carcinoma cell proliferation<sup>74,75</sup></li> <li>- Inhibits the metastasis of cervical cancer<sup>76</sup></li> <li>- Supportive pharmaceutical applications for acute lung injury treatment<sup>77</sup></li> <li>- Pharmaceutical for osteoarthritis-induced joint injury treatment<sup>78</sup></li> </ul> | <ul style="list-style-type: none"> <li>- Burn wound healing via angiogenesis promotion<sup>79</sup></li> </ul>                                                                                       | -                                                                                                                                                                                                                                                     |
| <b>Acteoside</b><br>          | 61276-17-3  | <ul style="list-style-type: none"> <li>- Anti-inflammatory</li> <li>- Antioxidative</li> <li>- Induces apoptosis</li> <li>- Inhibits proliferation</li> <li>- Neuroprotective</li> <li>- Antimicrobial</li> </ul> | <ul style="list-style-type: none"> <li>- Induces cancer cell apoptosis, e.g., colon cancer cells<sup>80</sup></li> <li>- Protects neurons against injury leading to Alzheimer's disease<sup>81</sup></li> <li>- Active factor against respiratory syncytial virus<sup>81</sup></li> </ul>                                                                                           | <ul style="list-style-type: none"> <li>- Protects skin fibroblasts from UV radiation and X-ray radiation<sup>82,83</sup></li> </ul>                                                                  | -                                                                                                                                                                                                                                                     |
| <b>Ginkgolic acid</b><br>     | 22910-60-7  | <ul style="list-style-type: none"> <li>- Induces apoptosis</li> <li>- Reduces tumor growth</li> <li>- Antimicrobial</li> <li>- Anti-inflammatory</li> </ul>                                                       | <ul style="list-style-type: none"> <li>- Antidiabetic treatment<sup>84</sup></li> <li>- Induces cancer cell apoptosis<sup>85</sup></li> <li>- Inhibits formation of bacterial biofilms<sup>86</sup></li> </ul>                                                                                                                                                                      | -                                                                                                                                                                                                    | <ul style="list-style-type: none"> <li>- Prevents the formation of <i>E. coli</i> bacterial biofilms<sup>86</sup></li> </ul>                                                                                                                          |

Table 2. Extraction of Phenolic Compounds Using Deep Eutectic Solvents<sup>a</sup>

| biomass (part)                                | DES                               | molar ratio | method of extraction | temp [°C] | water content [%] | time [min] | extracted compd        | yield (calcd on 1 g of dry biomass) | ref |
|-----------------------------------------------|-----------------------------------|-------------|----------------------|-----------|-------------------|------------|------------------------|-------------------------------------|-----|
| <i>Vitis rotundifolia</i> (fruit skins)       | ChCl:lactic acid                  | 1:2         | UAE                  | 60        | 20                | 30         | ellagic acid           | 21300 µg/g                          | 87  |
|                                               | ChCl:oxalic acid                  | 1:1         | UAE                  | 60        | 30                | 30         | ellagic acid           | 16000 µg/g                          |     |
|                                               | ChCl:lactic acid                  | 1:2         | UAE                  | 60        | 20                | 30         | gallic acid            | 10300 µg/g                          |     |
|                                               | ChCl:oxalic acid                  | 1:1         | UAE                  | 60        | 30                | 30         | gallic acid            | 10400 µg/g                          |     |
| <i>Olea europaea</i> L. (leaves)              | ChCl:acetic acid                  | 1:1         | SAE                  | 50        | 20                | 180        | total phenolic content | 470 µg GA/g <sup>b</sup>            | 88  |
|                                               | ChCl:malic acid                   | 1:1         | SAE                  | 50        | 20                | 180        | total phenolic content | 260 µg GA/g <sup>b</sup>            |     |
|                                               | ChCl:malonic acid                 | 1:1         | SAE                  | 50        | 20                | 180        | total phenolic content | 250 µg GA/g <sup>b</sup>            |     |
|                                               | ChCl:citric acid                  | 2:1         | SAE                  | 50        | 20                | 180        | total phenolic content | 240 µg GA/g <sup>b</sup>            |     |
| <i>Solanum lycopersicum</i> (fruit peels)     | ChCl:1,2-propanediol              | 1:2         | UAE                  | 65        | 10                | 60         | caffeic acid           | 2 µg/g                              | 89  |
|                                               | ChCl:1,2-propanediol              | 1:2         | UAE                  | 65        | 10                | 60         | chlorogenic acid       | 37 µg/g                             |     |
|                                               | ChCl:1,2-propanediol              | 1:2         | UAE                  | 65        | 10                | 60         | gallic acid            | 10 µg/g                             |     |
|                                               | ChCl:lactic acid                  | 1:2         | UAE                  | 65        | 10                | 60         | caffeic acid           | 5 µg/g                              |     |
|                                               | ChCl:lactic acid                  | 1:2         | UAE                  | 65        | 10                | 60         | chlorogenic acid       | 52 µg/g                             |     |
|                                               | ChCl:lactic acid                  | 1:2         | UAE                  | 65        | 10                | 60         | gallic acid            | 14 µg/g                             |     |
| <i>Apocynum ventem</i> L. (leaves)            | ChCl:levulinic acid               | 1:2         | SAE                  | 50        | 45                | 30         | gallic acid            | 1009 µg/g                           | 90  |
|                                               | ChCl:levulinic acid               | 1:2         | SAE                  | 50        | 45                | 30         | protocatechuic acid    | 418 µg/g                            |     |
|                                               | ChCl:levulinic acid               | 1:2         | MAE                  | —         | 45                | 0.5        | gallic acid            | 924 µg/g                            |     |
|                                               | ChCl:levulinic acid               | 1:2         | MAE                  | —         | 45                | 0.5        | protocatechuic acid    | 575 µg/g                            |     |
| Brewer's spent grain                          | ChCl:glycerol                     | 1:2         | MAE                  | —         | 25                | 20         | total phenolic content | 3780 µg GA/g <sup>b</sup>           | 91  |
|                                               | ChCl:ethylene glycol              | 1:2         | MAE                  | —         | 25                | 20         | total phenolic content | 2150 µg GA/g <sup>b</sup>           |     |
| <i>Leptospermum scoparium</i> (leaves)        | ChCl:ethylene glycol              | 1:2         | SAE                  | RT        | 0                 | 60         | total phenolic content | 56870 µg GA/g <sup>b</sup>          | 92  |
|                                               | ChCl:1,3-propanediol              | 1:3         | SAE                  | RT        | 0                 | 60         | total phenolic content | 50670 µg GA/g <sup>b</sup>          |     |
|                                               | ChCl:lactic acid                  | 1:2         | SAE                  | RT        | 0                 | 60         | total phenolic content | 52520 µg GA/g <sup>b</sup>          |     |
|                                               | ChCl:acetic acid                  | 1:2         | SAE                  | RT        | 0                 | 60         | total phenolic content | 32490 µg GA/g <sup>b</sup>          |     |
| <i>Lavandula angustifolia</i> (flowers)       | ChCl:glycerol                     | 1:2         | UAE                  | 40        | 30                | 30         | total phenolic content | 44650 µg GA/g <sup>b</sup>          | 93  |
|                                               | ChCl:glycerol                     | 1:3         | UAE                  | 40        | 30                | 30         | total phenolic content | 41460 µg GA/g <sup>b</sup>          |     |
|                                               | ChCl:glycerol                     | 1:4         | UAE                  | 40        | 30                | 30         | total phenolic content | 40750 µg GA/g <sup>b</sup>          |     |
| <i>Lilium lancifolium</i> Thunb. (bulbs)      | ChCl:ethylene glycol              | 1:2         | SAE                  | 50        | 20                | 40         | regaloside C           | 310 µg/g                            | 94  |
|                                               | ChCl:ethylene glycol              | 1:2         | SAE                  | 50        | 20                | 40         | regaloside E           | 290 µg/g                            |     |
|                                               | ChCl:ethylene glycol              | 1:2         | SAE                  | 50        | 20                | 40         | regaloside B           | 3040 µg/g                           |     |
| <i>Plantago asiatica</i> L. (aerial part)     | ChCl:lactic acid:ethylene glycol  | 1:4:2       | UAE                  | 60        | 50                | 35         | plantamajoside         | 3830 µg/g                           | 95  |
|                                               | ChCl:lactic acid:ethylene glycol  | 1:4:2       | UAE                  | 60        | 50                | 35         | acteoside              | 4230 µg/g                           |     |
| <i>Sanghuangporus baumii</i> (fruiting body)  | ChCl:malic acid                   | 1:2         | UAE                  | 50        | 40                | 30         | total phenolic content | 6370 µg GA/g <sup>b</sup>           | 96  |
| <i>Polygonum aviculare</i> (leaves)           | ChCl:levulinic acid               | 1:2         | UAE                  | 70        | 38                | 60         | gallic acid            | 39800 µg/g                          | 97  |
|                                               | ChCl:levulinic acid               | 1:2         | UAE                  | 70        | 38                | 60         | 5-caffeoylquinic acid  | 11830 µg/g                          |     |
| <i>Eucommia ulmoides</i> (leaves)             | ChCl:levulinic acid               | 1:2         | UAE                  | 70        | 38                | 60         | chlorogenic acid       | 7160 µg/g                           | 98  |
|                                               | ChCl:1,4-butanediol:ascorbic acid | 1:1:0.1     | MAE                  | —         | 20                | 20         | chlorogenic acid       | 3659 µg/g                           |     |
| <i>Achillea millefolium</i> L. (aerial parts) | ChCl:lactic acid                  | 1:2         | UAE                  | 50        | 25                | 30         | chlorogenic acid       | 2970 µg/g                           | 99  |
|                                               | ChCl:urea                         | 2:1         |                      |           |                   |            |                        | 2900 µg/g                           |     |

Table 2. continued

| biomass (part)                        | DES                  | molar ratio | method of extraction | temp [°C] | water content [%] | time [min] | extracted compd        | yield (calcd on 1 g of dry biomass) | ref |
|---------------------------------------|----------------------|-------------|----------------------|-----------|-------------------|------------|------------------------|-------------------------------------|-----|
| <i>Mentha piperita</i> (leaves)       | ChCl:glycerol        | 1:1         | SAE                  | 60        | 30                | 30         | chlorogenic acid       | 160 µg/g                            | 100 |
|                                       | ChCl:glycerol        | 1:1         | SAE                  | 60        | 30                | 30         | rosmarinic acid        | 3233 µg/g                           |     |
|                                       | ChCl:citric acid     | 1:1         | SAE                  | 60        | 30                | 30         | chlorogenic acid       | 206 µg/g                            |     |
|                                       | ChCl:citric acid     | 1:1         | SAE                  | 60        | 30                | 30         | rosmarinic acid        | 12005 µg/g                          |     |
| <i>Rhus coriaria</i> L. (fruits)      | ChCl:lactic acid     | 1:2         | UAE                  | 25        | 20                | 30         | total phenolic content | 124960 µg GA/g <sup>b</sup>         | 101 |
|                                       | ChCl:acetic acid     | 1:2         | UAE                  | 25        | 20                | 30         | total phenolic content | 119570 µg GA/g <sup>b</sup>         |     |
| <i>Ginkgo biloba</i> (leaves)         | ChCl:ascorbic acid   | 1:1         | UAE                  | 70        | 30                | 30         | ginkgolic acid         | 10434 µg/g                          | 102 |
| <i>Malus domestica</i> (fruit pomace) | ChCl:fructose        | 1:1         | UAE                  | 70        | 30                | 30         | ginkgolic acid         | 8155 µg/g                           | 103 |
|                                       | ChCl:glycerol        | 1:2         | UAE                  | 30        | 30                | 30         | total phenolic content | 5600 µg GA/g <sup>b</sup>           |     |
|                                       | ChCl:citric acid     | 1:1         | UAE                  | 30        | 30                | 30         | total phenolic content | 4600 µg GA/g <sup>b</sup>           |     |
| <i>Mentha piperita</i> (leaves)       | ChCl:glycerol        | 1:2         | SAE                  | 70        | 20                | 180        | rosmarinic acid        | 5090 µg/g                           | 104 |
| <i>Curcuma longa</i> L. (rhizomes)    | ChCl:citric acid     | 1:1         | MAE                  | 30        | 30                | 6          | curcuminoids           | 89870 µg/g                          | 105 |
| <i>Phoenix dactylifera</i> L. (seeds) | ChCl:lactic acid     | 1:2         | UAE                  | 40        | 30                | 15         | total phenolic content | 145540 µg GA/g <sup>b</sup>         | 106 |
| <i>Cosmos sulphureus</i> (seeds)      | ChCl:lactic acid     | 1:2         | UAE                  | 47.5      | 32.6              | 40         | total phenolic content | 35300 µg GA/g <sup>b</sup>          | 107 |
| <i>Curcuma longa</i> L. (rhizomes)    | ChCl:malonic acid    | 1:1         | UAE                  | 90        | 50                | 60         | curcuminoids           | 165510 µg/g                         | 108 |
|                                       | ChCl:propionic acid  | 1:2         | UAE                  | 90        | 50                | 60         | curcuminoids           | 120920 µg/g                         |     |
|                                       | ChCl:oxalic acid     | 1:1         | UAE                  | 90        | 50                | 60         | curcuminoids           | 112210 µg/g                         |     |
|                                       | ChCl:ethylene glycol | 1:2         | UAE                  | 90        | 50                | 60         | curcuminoids           | 50870 µg/g                          |     |

<sup>a</sup>RT, room temperature; GA, gallic acid; UAE, ultrasound-assisted extraction; MAE, microwave-assisted extraction; SAE, stirring-assisted extraction. <sup>b</sup>Mass of all phenolic compounds, calculated as mass of the gallic acid.

DESs, as well as the influence of their structures on the efficiency of extraction, is thoroughly discussed. Additionally, technological aspects, including the influence of additives, the extraction system, and conditions, are discussed. The newest solutions of the crucial problem concerning solute recovery after extraction and DES recycling are also presented. Further perspectives, taking into account the strengths and weaknesses of extraction using DESs, are also discussed.

## 2. THE MOST INTERESTING BIOACTIVE COMPOUNDS EXTRACTED WITH DESs FROM PLANT MATERIAL

The most interesting, widely investigated plant ingredients belong to one of the following groups: phenolics, flavonoids, terpenoids, saponins, polysaccharides, or alkaloids. Each group contains many bioactive compounds with interesting properties, which makes them promising chemicals for the pharmaceutical, cosmetic, and food industries. In this section, the properties and potencies of the compounds most frequently mentioned in the recent literature are presented.

**2.1. Phenolic Compounds.** Phenolic compounds can be successfully extracted from plants occurring in all habitats. It is also worth mentioning that the majority of them are already known for their interesting properties that are useful in medicine, foods, or cosmetics. They are edible, e.g., found in tomatoes, olives, grapes, common purslane, and common knotgrass; or they are part of the group of herbs, e.g., mint, lavender, and *Plantago asiatica*.<sup>34,35</sup> The antimicrobial activities and perspectives of phenolic applications as food preservatives or biocides are widely discussed.<sup>36</sup> Phenolics such as chlorogenic acid, gallic acid, caffeic acid, and rosmarinic acid

are secondary metabolites in plants.<sup>37</sup> Because of their antioxidant and anti-inflammatory properties, they can be used as active ingredients in the cosmetic, food, and pharmaceutical industries.<sup>38–40</sup> Table 1 presents the newest findings in the bioactivities and possible future applications of the chosen phenolic compounds extracted from plants.<sup>41–86</sup> Based on the information presented in Table 1, it is clear that current research focuses mostly on the medical application of phenolics in anticancer preparations. It is worth mentioning that phenolics have shown activities in the treatment of other civilization and neurodegenerative diseases.

The extraction of phenolic compounds has been widely discussed in the literature. Scientists are attempting to replace classic methods with more ecologically sound methods. An overview of the newest findings in the extraction of these valuable compounds from different types of plant materials using DESs is presented in Table 2. Several factors (the molar ratio of the HBD and HBA in DES, the method of extraction, the temperature, water addition, and the time of extraction) influencing the efficiency of the process are included.<sup>87–108</sup>

The yields of extracted chemicals depend on a few factors. The major factor is the type of plant and the contents of the active compounds. However, some trends in the influences of other factors can also be observed. When the type of HBD in the DES is considered, the application of an acidic HBD, rather than polyalcohols and sugars, is more favorable. For instance, in an extraction from *Solanum lycopersicum*, higher yields of gallic acid, chlorogenic acid, and caffeic acid were obtained while using DES ChCl:lactic acid, compared to ChCl:1,2-propanediol (for gallic acid, the difference was 4 µg/g; for chlorogenic acid, 15 µg/g; and for caffeic acid, 3 µg/g).<sup>89</sup> The

Table 3. Chemical Structures, Properties, and Application of Flavonoids Present in Plants

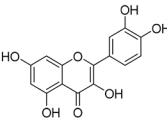
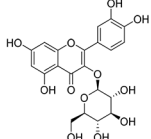
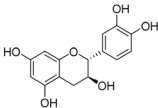
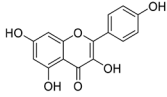
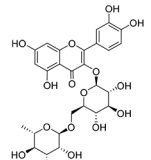
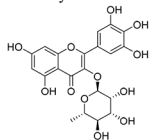
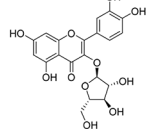
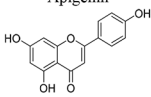
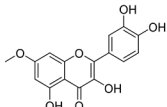
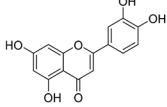
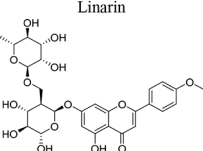
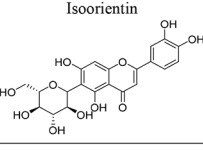
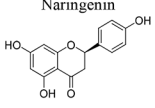
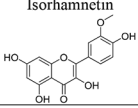
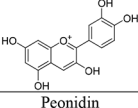
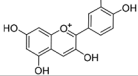
| Name and chemical structure                                                                              | CAS number | Activity                                                                                                                                                              | Applications/potential applications                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                              |
|----------------------------------------------------------------------------------------------------------|------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                          |            |                                                                                                                                                                       | Pharmaceuticals industry                                                                                                                                                                                                                                                                                                                                                                        | Cosmetics industry                                                                                                                                                                                             | Food industry                                                                                                                                                                                                                                                                                                |
| <b>Quercetin</b><br>    | 117-39-5   | <ul style="list-style-type: none"> <li>- Antimicrobial</li> <li>- Antiviral</li> <li>- Antioxidative</li> </ul>                                                       | <ul style="list-style-type: none"> <li>- Blocks virus propagation by inhibiting virus proteases<sup>112</sup></li> <li>- Enhances antiviral drug activity, e.g., acyclovir<sup>113</sup></li> <li>- Inhibits proliferation and migration of osteosarcoma cells<sup>114,115</sup></li> <li>- Has positive effects against SARS-CoV-2 (in molecular docking simulations)<sup>116</sup></li> </ul> | <ul style="list-style-type: none"> <li>- Hyperpigmentation disorders treatment<sup>117</sup></li> </ul>                                                                                                        | <ul style="list-style-type: none"> <li>- Increases antimicrobial resistance of corn starch<sup>118</sup></li> <li>- Food packaging additive that protects products from UV light<sup>119</sup></li> <li>- Food packaging additive that changes color according to product freshness<sup>120</sup></li> </ul> |
| <b>Isoquercetin</b><br> | 482-35-9   | <ul style="list-style-type: none"> <li>- Antiviral</li> <li>- Antioxidative</li> </ul>                                                                                | <ul style="list-style-type: none"> <li>- Inhibits proliferation of influenza viral proteins<sup>120</sup></li> <li>- Strong antioxidative activity<sup>121</sup></li> <li>- Inhibits growth of liver cancer cells (HepG2 cell line)<sup>122</sup></li> </ul>                                                                                                                                    | <ul style="list-style-type: none"> <li>- Anti-aging and anti-wrinkle properties<sup>123</sup></li> </ul>                                                                                                       | -                                                                                                                                                                                                                                                                                                            |
| <b>Catechin</b><br>     | 18829-70-4 | <ul style="list-style-type: none"> <li>- Antioxidative</li> <li>- Antimicrobial</li> </ul>                                                                            | <ul style="list-style-type: none"> <li>- Inhibits cancer cell growth<sup>124,125</sup></li> </ul>                                                                                                                                                                                                                                                                                               | <ul style="list-style-type: none"> <li>- Protects skin from UV radiation<sup>126</sup></li> <li>- Anti-aging properties<sup>127</sup></li> </ul>                                                               | <ul style="list-style-type: none"> <li>- Delays growth of molds on fruits<sup>125</sup></li> </ul>                                                                                                                                                                                                           |
| <b>Kaempferol</b><br>  | 520-18-3   | <ul style="list-style-type: none"> <li>- Induces autophagic cancer cell death</li> <li>- Antioxidative</li> <li>- Antimicrobial</li> <li>- Neuroprotective</li> </ul> | <ul style="list-style-type: none"> <li>- Prevents migration of cancer cells and enhances their autophagic death<sup>128,129</sup></li> <li>- Inhibits progression of neurological diseases, e.g., Alzheimer's disease, Parkinson's disease, epilepsy, anxiety disorders<sup>130</sup></li> </ul>                                                                                                | <ul style="list-style-type: none"> <li>- Drug in skin dermal fibroblastic inflammation treatment<sup>131</sup></li> <li>- Anti-wrinkle activity (in tetrasaccharides form)<sup>132</sup></li> </ul>            | <ul style="list-style-type: none"> <li>- Limits synthesis of toxic biogenic amines by bacteria present in fish and meat<sup>133</sup></li> </ul>                                                                                                                                                             |
| <b>Rutin</b><br>      | 153-18-4   | <ul style="list-style-type: none"> <li>- Induces apoptosis</li> <li>- Antioxidative</li> <li>- Neuroprotective</li> </ul>                                             | <ul style="list-style-type: none"> <li>- Inhibits angiogenesis and proliferation of cancer cells, determines their apoptosis<sup>134-136</sup></li> <li>- Limits neurotoxicity of other drugs (e.g., polymyxin)<sup>137</sup></li> </ul>                                                                                                                                                        | <ul style="list-style-type: none"> <li>- Suppresses skin diseases, e.g., redness, allergic contact dermatitis, atopic dermatitis<sup>138</sup></li> </ul>                                                      | -                                                                                                                                                                                                                                                                                                            |
| <b>Myricitrin</b><br> | 17912-87-7 | <ul style="list-style-type: none"> <li>- Neuroprotective</li> <li>- Antioxidative</li> </ul>                                                                          | <ul style="list-style-type: none"> <li>- Attenuates neuroinflammation<sup>139</sup></li> <li>- Hepatoprotective agent<sup>140</sup></li> <li>- Inhibits African swine fever virus protease<sup>141</sup></li> </ul>                                                                                                                                                                             | -                                                                                                                                                                                                              | -                                                                                                                                                                                                                                                                                                            |
| <b>Avicularin</b><br> | 572-30-5   | <ul style="list-style-type: none"> <li>- Antioxidative</li> <li>- Anti-inflammatory</li> <li>- Neuroprotective</li> </ul>                                             | <ul style="list-style-type: none"> <li>- Inhibits Alzheimer's disease progression<sup>142</sup></li> <li>- Candidiasis treatment<sup>143</sup></li> </ul>                                                                                                                                                                                                                                       | -                                                                                                                                                                                                              | -                                                                                                                                                                                                                                                                                                            |
| <b>Apigenin</b><br>   | 520-36-5   | <ul style="list-style-type: none"> <li>- Antioxidative</li> <li>- Induces apoptosis</li> <li>- Neuroprotective</li> </ul>                                             | <ul style="list-style-type: none"> <li>- Active compound against cancer cell lines (e.g., colon, breast cancer)<sup>144,145</sup></li> <li>- Prevents diabetic complications<sup>146</sup></li> <li>- Anti-Parkinson's disease activity<sup>147</sup></li> <li>- Improves cardiac function<sup>148</sup></li> </ul>                                                                             | <ul style="list-style-type: none"> <li>- Prevents skin from UV photodamage<sup>149</sup></li> <li>- Enhances wound healing<sup>149</sup></li> <li>- Enhances lipid production in skin<sup>150</sup></li> </ul> | <ul style="list-style-type: none"> <li>- Preservative in soy protein isolate<sup>151</sup></li> </ul>                                                                                                                                                                                                        |
| <b>Rhamnetin</b><br>  | 90-19-7    | <ul style="list-style-type: none"> <li>- Anti-inflammatory</li> <li>- Antimicrobial</li> </ul>                                                                        | <ul style="list-style-type: none"> <li>- Antibacterial drug for sepsis treatment<sup>152</sup></li> <li>- Inhibits cancer cell proliferation (e.g., breast cancer)<sup>153</sup></li> </ul>                                                                                                                                                                                                     | <ul style="list-style-type: none"> <li>- Skin whitening agent<sup>154</sup></li> </ul>                                                                                                                         | -                                                                                                                                                                                                                                                                                                            |
| <b>Luteolin</b><br>   | 491-70-3   | <ul style="list-style-type: none"> <li>- Antiviral</li> </ul>                                                                                                         | <ul style="list-style-type: none"> <li>- Has positive effect against SARS-CoV-2 virus (examined via molecular docking simulations and in vivo tests)<sup>155,156</sup></li> <li>- In glucoside form, has high anti-inflammatory activity<sup>157</sup></li> <li>- Inhibits activity of <math>\alpha</math>-glucosidase—glycemic control<sup>158</sup></li> </ul>                                | <ul style="list-style-type: none"> <li>- Cellular melanin synthesis control agent (in the form of luteolin-7-sulfate)<sup>159</sup></li> </ul>                                                                 | <ul style="list-style-type: none"> <li>- Limits synthesis of toxic biogenic amines by bacteria present in fish and meat<sup>133</sup></li> </ul>                                                                                                                                                             |

Table 3. continued

| Name and chemical structure                                                                       | CAS number | Activity                                                                                                                  | Applications/potential applications                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                          |                                                                                                                                                                                                                                           |
|---------------------------------------------------------------------------------------------------|------------|---------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                   |            |                                                                                                                           | Pharmaceuticals industry                                                                                                                                                                                                                                                                                                                                                                | Cosmetics industry                                                                                                                                                                       | Food industry                                                                                                                                                                                                                             |
| <br>Linarin      | 480-36-4   | <ul style="list-style-type: none"> <li>- Antioxidative</li> <li>- Anti-inflammatory</li> </ul>                            | <ul style="list-style-type: none"> <li>- Protective against osteoporosis caused by cadmium<sup>160</sup></li> <li>- Inhibits COX-2 inflammation pathway<sup>161</sup></li> <li>- Improves insulin and glucose tolerance<sup>162</sup></li> <li>- Sleep-enhancing medicament<sup>163</sup></li> <li>- Reduces neuron death caused by H<sub>2</sub>O<sub>2</sub><sup>164</sup></li> </ul> | <ul style="list-style-type: none"> <li>- Enhances melanogenesis—hypopigmentation disorders treatment<sup>165</sup></li> </ul>                                                            | -                                                                                                                                                                                                                                         |
| <br>Isoorientin  | 4261-42-1  | <ul style="list-style-type: none"> <li>- Antioxidative</li> <li>- Photoprotective</li> <li>- Induces apoptosis</li> </ul> | <ul style="list-style-type: none"> <li>- Osteoporosis treatment<sup>166</sup></li> <li>- Induces gastric cell apoptosis by increasing the amount of free radicals in cancer cells and decreasing them in healthy cells<sup>167</sup></li> </ul>                                                                                                                                         | <ul style="list-style-type: none"> <li>- Photoprotective agent—the SPF (sun protection factor) of sample (0.01% concentration of isoorientin) reached nearly 17<sup>168</sup></li> </ul> | -                                                                                                                                                                                                                                         |
| <br>Naringenin   | 480-41-1   | <ul style="list-style-type: none"> <li>- Antimicrobial</li> <li>- Induces apoptosis</li> </ul>                            | <ul style="list-style-type: none"> <li>- Inhibits proliferation and induces apoptosis of cancer cells<sup>169,170</sup></li> </ul>                                                                                                                                                                                                                                                      | -                                                                                                                                                                                        | <ul style="list-style-type: none"> <li>- Prevents the growth of <i>S. aureus</i> bacteria on food products<sup>171</sup></li> <li>- Protects tobacco crops from disease caused by <i>Phytophthora nicotianae</i><sup>172</sup></li> </ul> |
| <br>Isorhamnetin | 480-19-3   | <ul style="list-style-type: none"> <li>- Antioxidative</li> </ul>                                                         | <ul style="list-style-type: none"> <li>- Anti-obesity agent<sup>173</sup></li> <li>- Regulates insulin pathway<sup>174</sup></li> </ul>                                                                                                                                                                                                                                                 | <ul style="list-style-type: none"> <li>- Inhibits melanogenesis<sup>175</sup></li> </ul>                                                                                                 | -                                                                                                                                                                                                                                         |
| <br>Cyanidin     | 13306-05-3 | <ul style="list-style-type: none"> <li>- Antioxidative</li> <li>- Anti-inflammatory</li> </ul>                            | <ul style="list-style-type: none"> <li>- Protects neurons from oxidative damage<sup>176</sup></li> <li>- Protects cardiovascular vessels<sup>177</sup></li> <li>- Osteoporosis treatment<sup>178</sup></li> </ul>                                                                                                                                                                       | <ul style="list-style-type: none"> <li>- Protects skin cells from oxidative damage (in the glucoside form)<sup>179</sup></li> </ul>                                                      | <ul style="list-style-type: none"> <li>- Intelligent food packaging<sup>180</sup></li> </ul>                                                                                                                                              |
| <br>Peonidin    | 134-01-0   | <ul style="list-style-type: none"> <li>- Antioxidative</li> </ul>                                                         | <ul style="list-style-type: none"> <li>- Prebiotic activity and antimicrobial activity against foodborne bacteria<sup>181</sup></li> </ul>                                                                                                                                                                                                                                              | -                                                                                                                                                                                        | -                                                                                                                                                                                                                                         |

same phenomenon was observed in the isolation of rosmarinic acid from *Mentha piperita*. The DES ChCl: citric acid was much more efficient than ChCl: glycerol (the yield was 8800  $\mu\text{g/g}$  higher).<sup>99</sup> Similar results were observed by Alrugaibah et al.<sup>87</sup> The extraction of ellagic acid from *Vitis rotundifolia* was much more efficient with DES ChCl: lactic acid (21.3 mg/g of dry biomass) and ChCl: oxalic acid (16.0 mg/g), compared to ChCl: 1,2-propanediol (8.4 mg/g).

The other important issue in the extraction of phenolics with DESs is the chosen technique. As can be seen in Table 2, ultrasound- or microwave-assisted processes allow for a reduced time of extraction and a high yield of the desired chemical to be obtained. For example, in the microwave extraction of protocatechuic acid from *Apocynum ventem* L. with the DES ChCl: levulinic acid, a yield of 575  $\mu\text{g/g}$  was obtained in 30 s, while traditional stirring extraction required 30 min to obtain 418  $\mu\text{g/g}$ .<sup>90</sup>

**2.2. Flavonoids.** Flavonoids can also be considered as phenolic compounds, but because of their distinctive chemical structures, based on 2-phenyl-chromone, they are presented separately.<sup>109</sup> Similar to phenolics, flavonoids can be found in plants from all over the world, especially in edible ones. The richest sources are fruits from *Prunus* (e.g., cherry and plum) and *Vaccinium* (e.g., cranberry and blueberry) species. There have also been many attempts to utilize byproducts or wastes from the forestry and food industries. An interesting example is the utilization of bark from *Larix decidua* (European larch), which is a byproduct of timber production. Studies revealed that it can be a promising and cheap source of flavonoids.<sup>110,111</sup> Flavonoids have great potential as anticancer and anti-inflammatory pharmaceuticals, as well as antiaging

agents in cosmetics. Examples of these compounds, extracted from plants with DESs, are presented in Table 3.<sup>46,112–181</sup>

Flavonoids are commonly presented as glycosides, such as cyanidin-3-*O*-glucoside and quercetin 3-rutinoside, because of their increased efficiencies as pharmaceuticals. After glycosylation their water solubilities and stabilities are enhanced, which improves their bioavailability.<sup>182</sup>

Natural flavonoids have also been studied as additives/preservatives in the food industry. They have very good antioxidative and antimicrobial properties, which makes them promising natural preservatives. Examples of flavonoid extraction with DESs from plant material are presented in Table 4.<sup>89,90,95,97,98,100,104,183–196</sup>

As can be seen from Table 4, there is no clear tendency for the influence of DES composition on the yield of flavonoids. For example, in the extraction of quercetin from tomatoes, the yield was similar for DES with acidic and diol HBDs (1.02  $\mu\text{g/g}$  for DES ChCl: 1,2-propanediol and 1.47  $\mu\text{g/g}$  for ChCl: lactic acid).<sup>89</sup> In some cases, better results were obtained in an extraction with DES containing diols compared to other HBDs (e.g., the yield of rutin extracted from *Fagopyrum esculentum* with ChCl: triethylene glycol was higher than that extracted with ChCl: urea; the difference was 380  $\mu\text{g/g}$ ).<sup>188</sup>

**2.3. Terpenes, Terpenoids, and Saponins.** Another class of compounds with great importance is terpenes and their derivatives—terpenoids are considered to be one of the most diverse groups of plant metabolites.<sup>168</sup> They are present in many plants and in some marine organisms. A unique feature of all terpenes is a chemical structure based on isoprene molecules. Many of them have pharmacological activities—anticancer, antimicrobial, and anti-inflammatory.<sup>169,170</sup> Be-

Table 4. Extraction of Flavonoids Using Deep Eutectic Solvents

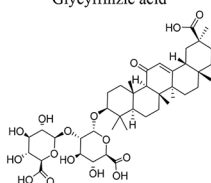
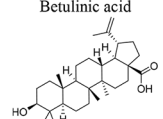
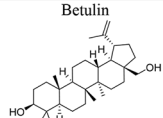
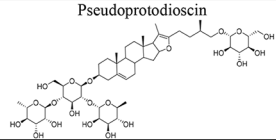
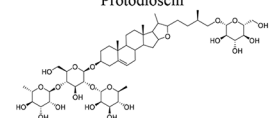
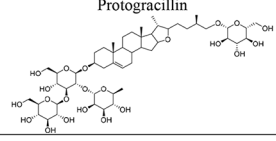
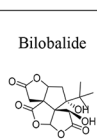
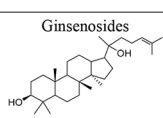
| biomass                                    | DES                               | molar ratio | method of extraction <sup>a</sup> | temp [°C] | water content [%] | time [min] | extracted compd            | yield (calcd on 1 g of dry biomass) | ref |
|--------------------------------------------|-----------------------------------|-------------|-----------------------------------|-----------|-------------------|------------|----------------------------|-------------------------------------|-----|
| <i>Polygonatum odoratum</i> (rhizomes)     | ChCl:malic acid                   | 1:1         | UAE                               | 50        | 0                 | 20         | total flavonoid content    | 4760 µg/g                           | 183 |
|                                            | ChCl:citric acid                  | 1:1         | UAE                               | 50        | 0                 | 20         | total flavonoid content    | 6830 µg/g                           |     |
|                                            | ChCl:lactic acid                  | 1:1         | UAE                               | 50        | 0                 | 20         | total flavonoid content    | 7320 µg/g                           |     |
| <i>Larix decidua</i> (bark)                | ChCl:urea                         | 1:2         | SAE                               | 58        | 75                | 94         | total flavonoid content    | 159000 µg/g                         | 184 |
|                                            | ChCl:urea                         | 1:2         | SAE                               | 58        | 50                | 94         | total flavonoid content    | 305000 µg/g                         |     |
|                                            | ChCl:urea                         | 1:2         | SAE                               | 58        | 25                | 94         | total flavonoid content    | 275000 µg/g                         |     |
|                                            | ChCl:1,4-butanediol               | 1:2         | SAE                               | 58        | 75                | 94         | total flavonoid content    | 376000 µg/g                         |     |
| <i>Polygonatum sibiricum</i> (whole plant) | ChCl:1,4-butanediol               | 1:2         | SAE                               | 58        | 50                | 94         | total flavonoid content    | 376000 µg/g                         | 185 |
|                                            | ChCl:1,4-butanediol               | 1:2         | SAE                               | 58        | 25                | 94         | total flavonoid content    | 383000 µg/g                         |     |
|                                            | ChCl:lactic acid                  | 1:4         | UAE                               | 50        | 30                | 30         | total flavonoid content    | 3000 µg/g                           |     |
|                                            | ChCl:1,2-propanediol              | 1:2         | UAE                               | 65        | 10                | 60         | quercetin                  | 1.02 µg/g                           |     |
| <i>Solanum lycopersicum</i> (fruit peels)  | ChCl:lactic acid                  | 1:2         | UAE                               | 65        | 10                | 60         | quercetin                  | 1.47 µg/g                           | 89  |
|                                            | ChCl:levulinic acid               | 1:2         | SAE                               | 50        | 45                | 30         | catechin                   | 4338 µg/g                           |     |
|                                            | ChCl:levulinic acid               | 1:2         | SAE                               | 50        | 45                | 30         | rutin                      | 169 µg/g                            |     |
|                                            | ChCl:levulinic acid               | 1:2         | SAE                               | 50        | 45                | 30         | isoquercetin               | 2031 µg/g                           |     |
| <i>Apocynum ventem</i> L. (leaves)         | ChCl:levulinic acid               | 1:2         | MAE                               | —         | 45                | 0.5        | catechin                   | 5025 µg/g                           | 90  |
|                                            | ChCl:levulinic acid               | 1:2         | MAE                               | —         | 45                | 0.5        | rutin                      | 255 µg/g                            |     |
|                                            | ChCl:levulinic acid               | 1:2         | MAE                               | —         | 45                | 0.5        | isoquercetin               | 3411 µg/g                           |     |
|                                            | ChCl:lactic acid:ethylene glycol  | 1:4:2       | UAE                               | 60        | 50                | 35         | quercetin                  | 560 µg/g                            |     |
| <i>Plantago asiatica</i> L. (aerial part)  | ChCl:lactic acid:ethylene glycol  | 1:4:2       | UAE                               | 60        | 50                | 35         | kaempferol                 | 190 µg/g                            | 95  |
|                                            | ChCl:citric acid                  | 1:1         | MAE                               | —         | 40                | 2.5        | total anthocyanine content | 7864 µg/g                           |     |
| <i>Syzygium cumini</i> (fruits)            | ChCl:citric acid                  | 1:1         | UAE                               | 70        | 40                | 150        | total anthocyanine content | 8525 µg/g                           | 186 |
|                                            | ChCl:levulinic acid               | 1:2         | UAE                               | 70        | 38                | 60         | myricitrin                 | 10470 µg/g                          |     |
| <i>Polygonum aviculare</i> (leaves)        | ChCl:levulinic acid               | 1:2         | UAE                               | 70        | 38                | 60         | 3"-O-galloylmyricitrin     | 7920 µg/g                           | 97  |
|                                            | ChCl:levulinic acid               | 1:2         | UAE                               | 70        | 38                | 60         | quercitrin                 | 4260 µg/g                           |     |
| <i>Chrysanthemum indicum</i> L. (flowers)  | ChCl:levulinic acid               | 1:2         | UAE                               | 70        | 38                | 60         | avicularin                 | 3020 µg/g                           | 187 |
|                                            | ChCl:ethylene glycol              | 1:2         | UAE                               | RT        | 30                | 32         | linarin                    | 14230 µg/g                          |     |
|                                            | ChCl:urea                         | 1:2         | UAE                               | 40        | 20                | 40         | isoorientin                | 5110 µg/g                           |     |
|                                            | ChCl:triethylene glycol           | 1:4         | UAE                               | 40        | 20                | 40         | isoorientin                | 6660 µg/g                           |     |
| <i>Fagopyrum esculentum</i> (sprouts)      | ChCl:urea                         | 1:2         | UAE                               | 40        | 20                | 40         | rutin                      | 1840 µg/g                           | 188 |
|                                            | ChCl:triethylene glycol           | 1:4         | UAE                               | 40        | 20                | 40         | rutin                      | 2220 µg/g                           |     |
|                                            | ChCl:triethylene glycol           | 1:4         | UAE                               | RT        | 30                | 35         | quercetin                  | 383 µg/g                            |     |
|                                            | ChCl:1,2-propanediol              | 1:4         | UAE                               | RT        | 30                | 35         | naringenin                 | 48 µg/g                             |     |
| pollen typhae (pollen)                     | ChCl:1,2-propanediol              | 1:4         | UAE                               | RT        | 30                | 35         | kaempferol                 | 391 µg/g                            | 189 |
|                                            | ChCl:1,2-propanediol              | 1:4         | UAE                               | RT        | 30                | 35         | isorhamnetin               | 3149 µg/g                           |     |
|                                            | ChCl:1,2-propanediol              | 1:2         | UAE                               | 60        | 20                | 30         | cyanidin-3-galactoside     | 180 µg/g                            |     |
|                                            | ChCl:lactic acid                  | 1:2         | UAE                               | 60        | 20                | 30         | peonidin 3-arabinoside     | 320 µg/g                            |     |
| cranberry pomace                           | ChCl:lactic acid                  | 1:2         | UAE                               | 60        | 50                | 30         | cyanidin-3-galactoside     | 300 µg/g                            | 190 |
|                                            | ChCl:lactic acid                  | 1:2         | UAE                               | 60        | 50                | 30         | peonidin 3-arabinoside     | 600 µg/g                            |     |
|                                            | ChCl:lactic acid                  | 1:2         | UAE                               | 60        | 50                | 30         | peonidin 3-arabinoside     | 1143 µg/g                           |     |
|                                            | ChCl:1,4-butanediol:ascorbic acid | 1:1:0.2     | MAE                               | —         | 20                | 20         | rutin                      | 1143 µg/g                           |     |

Table 4. continued

| biomass                                                                                                                      | DES                               | molar ratio | method of extraction <sup>a</sup> | temp [°C] | water content [%] | time [min] | extracted compd         | yield (calcd on 1 g of dry biomass) | ref |
|------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-------------|-----------------------------------|-----------|-------------------|------------|-------------------------|-------------------------------------|-----|
| <i>Jaboticaba</i> processing byproduct                                                                                       | ChCl:1,4-butanediol:ascorbic acid | 1:1:0.2     | MAE                               | –         | 20                | 20         | isoquercetin            | 1087 µg/g                           | 191 |
|                                                                                                                              | ChCl:propylene glycol             | 1:2         | pressurized liquid extraction     | 90        | 53                | 12         | cyanidin-3-O-glucoside  | 29400 µg/g                          |     |
|                                                                                                                              | ChCl:malic acid                   | 1:2         | pressurized liquid extraction     | 90        | 53                | 12         | cyanidin-3-O-glucoside  | 25780 µg/g                          |     |
| <i>Buddleja globosa</i> (leaves)                                                                                             | ChCl:1,2-propanediol              | 1:3         | SAE                               | 60        | 20                | 20         | luteolin-7-O-glucoside  | 4387 µg/g                           | 192 |
| <i>Mentha piperita</i> (leaves)                                                                                              | ChCl:glycerol                     | 1:1         | SAE                               | 60        | 30                | 30         | luteolin-7-O-glucoside  | 5856 µg/g                           | 100 |
|                                                                                                                              | ChCl:glycerol                     | 1:1         | SAE                               | 60        | 30                | 30         | apigenin                | 361 µg/g                            |     |
|                                                                                                                              | ChCl:citric acid                  | 1:1         | SAE                               | 60        | 30                | 30         | luteolin 7-O-glucoside  | 7998 µg/g                           |     |
|                                                                                                                              | ChCl:citric acid                  | 1:1         | SAE                               | 60        | 30                | 30         | apigenin                | 384 µg/g                            |     |
|                                                                                                                              | ChCl:sucrose                      | 1:2         | UAE                               | RT        | 30                | 30         | rhamnetin-3-galactoside | 1470 µg/g                           |     |
| <i>Polygonum maritimum</i> L. (leaves and stems)<br>sour cherry pomace                                                       | ChCl:malic acid                   | 1:1         | SAE                               | 40        | 20                | 30         | quercetin-3-rutinoside  | 172 µg/g                            | 194 |
| <i>Potentilla Fruticosa</i> L. (leaves and stems)<br><i>Mentha piperita</i> (leaves)<br><i>Dendrobium officinale</i> (stems) | ChCl:malic acid                   | 1:1         | UAE                               | 40        | 20                | 30         | quercetin-3-rutinoside  | 119 µg/g                            | 195 |
|                                                                                                                              | ChCl:malic acid                   | 1:1         | MAE                               | –         | 20                | 0.25       | quercetin-3-rutinoside  | 138 µg/g                            |     |
|                                                                                                                              | ChCl:citric acid                  | 1:1         | UAE                               | 28        | 30                | 30         | catechin-7-O-glucoside  | 12200 µg/g                          |     |
|                                                                                                                              | ChCl:glycerol                     | 1:2         | SAE                               | 70        | 20                | 180        | hesperidin              | 3220 µg/g                           |     |
| <i>Dendrobium officinale</i> (stems)                                                                                         | ChCl:lactic acid                  | 1:4         | UAE                               | 50        | 30                | 40         | total flavonoid content | 35240 µg/g                          | 196 |

<sup>a</sup>UAE, ultrasound-assisted extraction; MAE, microwave-assisted extraction; SAE, stirring-assisted extraction.

Table 5. Chemical Structures, Properties, and Application of Terpenes, Terpenoids, and Saponins Present in Plants

| Name and chemical structure                                                                             | CAS number  | Activity                                                  | Applications/potential applications                                                                                                                                                                                                                            |                                                                |                                                                                                                                  |
|---------------------------------------------------------------------------------------------------------|-------------|-----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                         |             |                                                           | Pharmaceuticals industry                                                                                                                                                                                                                                       | Cosmetics industry                                             | Food industry                                                                                                                    |
| <br>Glycyrrhizic acid  | 1405-86-3   | - Anti-inflammatory<br>- Prevents coronavirus replication | - Has positive effects against SARS-CoV-2 virus <sup>200</sup><br>- Shows defensive effects against influenza viruses <sup>201</sup><br>- Regulates colorectal cancer oncogene <sup>202</sup>                                                                  | -                                                              | - Its nanofibrils can create stable emulsions <sup>203</sup><br>- Food sweetener <sup>203</sup>                                  |
| <br>Betulinic acid     | 472-15-1    | - Antimicrobial<br>- Antiparasitic                        | - Active against parasites (e.g., Leishmania, Plasmodium) - tropical diseases treatment <sup>204</sup><br>- Cancer treatment, e.g., leukemia, breast cancer, ovarian cancer, cervical cancer <sup>205</sup><br>- Shows activity against malaria <sup>206</sup> | -                                                              | - Antimicrobial food additive <sup>207</sup>                                                                                     |
| <br>Betulin            | 473-98-3    | - Induces apoptosis<br>- Anti-inflammatory                | - Inhibits COX-2 inflammatory pathway <sup>208</sup><br>- Induces apoptosis in cancer cells <sup>209</sup>                                                                                                                                                     | - Enhances wound healing <sup>210</sup>                        | -                                                                                                                                |
| <br>Pseudoprotodioscin | 102115-79-7 | - Cardiovascular diseases treatment                       | - Regulates cholesterol synthesis - cardiovascular diseases treatment <sup>211</sup>                                                                                                                                                                           | -                                                              | -                                                                                                                                |
| <br>Protodioscin       | 55056-80-9  | - Anti-inflammatory<br>- Induces apoptosis                | - Prevents cancer cell migration (e.g., bladder cancer cells) <sup>212</sup><br>- Enhances cervical cancer cell apoptosis <sup>213</sup>                                                                                                                       | - Inhibits activity of collagenase and elastase <sup>214</sup> | -                                                                                                                                |
| <br>Protogracillin    | 54848-30-5  | - Anti-inflammatory                                       | - Inflammatory diseases treatment <sup>215</sup>                                                                                                                                                                                                               | -                                                              | -                                                                                                                                |
| <br>Carnosic acid    | 3650-09-7   | - Antimicrobial<br>- Antioxidative<br>- Antiviral         | - High antioxidative activity <sup>216</sup><br>- Inhibits SARS-CoV-2 virus adsorption and replication <sup>217</sup>                                                                                                                                          | - Cosmetic preservative <sup>218</sup>                         | - Active against foodborne pathogens <sup>133</sup><br>- Effective preservative in meat, fish, and dairy products <sup>219</sup> |
| <br>Bilobalide       | 33570-04-6  | - Neuroprotective<br>- Anti-inflammatory                  | - Cerebral ischemic injury treatment <sup>220</sup><br>- Diseases caused by age-associated neurodegeneration treatment (e.g., Parkinson's disease, Alzheimer's disease) <sup>221</sup><br>- Acute lung injury treatment caused by sepsis <sup>222</sup>        | - Promotes collagen synthesis—anti-aging factor <sup>223</sup> | -                                                                                                                                |
| <br>Ginsenosides     | 74749-74-9  | - Anticancerous                                           | - Cancer treatment (e.g., lung cancer) <sup>224,225</sup>                                                                                                                                                                                                      | -                                                              | -                                                                                                                                |

cause of their diversity and interesting properties, they have become important ingredients in food, cosmetics, and pharmaceuticals. Their chemical synthesis is usually unprofitable or unsustainable, so efficient extraction from natural sources seems to be a very important direction in research and industrial development.<sup>197–199</sup> Table 5 presents a few examples of terpenes and terpenoids, with their activities and possible applications.<sup>133,200–225</sup>

The extraction of these groups of compounds from the plant material can be effectively carried out with DESs based on choline chloride as the HBA, summarized in Table 6.<sup>102,226–233</sup>

Licorice (*Glycyrrhiza glabra*) is one of the most commonly used plants, because of its high content of glycyrrhizic acid. In the isolation of terpenoids and saponins, the impact of HBDs in applied DESs is similar to the case of phenolic compound

extraction: higher yields of products are achieved with DESs when acidic HBDs are used. For example, in a process of bilobalide extraction from *Ginkgo biloba*, extraction with the DES ChCl:ascorbic acid yielded 7518  $\mu\text{g/g}$  product while in the presence of ChCl:fructose 6552  $\mu\text{g/g}$  was obtained.<sup>102</sup> Similar results were reported by Lanjekar and Rathod—the yield of glycyrrhizic acid obtained from licorice was nearly twice as high when succinic acid was the HBD, compared to DES with glycerol.<sup>226</sup>

**2.4. Other Chemicals Extracted from Plants with DESs.** There are many other interesting bioactive molecules that can be isolated from plants, apart from the mentioned phenolics, flavonoids, terpenoids, and saponins. Many of them present biological activities that are required by industries, especially the pharmaceutical industry. For instance, poly-

Table 6. Extraction of Terpenes, Terpenoids, and Saponins Using Deep Eutectic Solvents

| biomass                                      | DES                  | molar ratio | method of extraction <sup>a</sup> | temp [°C] | water content [%] | time [min] | extracted compd       | yield (calcd on 1 g of dry biomass) | ref |
|----------------------------------------------|----------------------|-------------|-----------------------------------|-----------|-------------------|------------|-----------------------|-------------------------------------|-----|
| <i>Glycyrrhiza glabra</i> (roots)            | ChCl:glycerol        | 1:1         | SAE                               | 30        | 15                | 60         | glycyrrhizic acid     | 23250 µg/g                          | 226 |
|                                              | ChCl:malic acid      | 1:1         | SAE                               | 30        | 15                | 60         | glycyrrhizic acid     | 36700 µg/g                          |     |
|                                              | ChCl:oxalic acid     | 1:1         | SAE                               | 30        | 15                | 60         | glycyrrhizic acid     | 39600 µg/g                          |     |
|                                              | ChCl:lactic acid     | 1:1         | SAE                               | 30        | 15                | 60         | glycyrrhizic acid     | 42820 µg/g                          |     |
|                                              | ChCl:succinic acid   | 1:1         | SAE                               | 30        | 15                | 60         | glycyrrhizic acid     | 43650 µg/g                          |     |
| <i>Glycyrrhiza glabra</i> (roots)            | ChCl:citric acid     | 1:1         | SAE                               | 30        | 15                | 60         | glycyrrhizic acid     | 30670 µg/g                          | 227 |
|                                              | ChCl:lactic acid     | 1:1         | SAE                               | 40        | 30                | 30         | glycyrrhizic acid     | 53720 µg/g                          |     |
| <i>Betula pendula</i> (bark)                 | ChCl:lactic acid     | 1:1         | SAE                               | 60        | 5.4               | 150        | betulinic acid        | 141 µg/g                            | 228 |
|                                              | ChCl:lactic acid     | 1:1         | SAE                               | 80        | 5.4               | 150        | betulinic acid        | 263 µg/g                            |     |
|                                              | ChCl:lactic acid     | 1:1         | SAE                               | 60        | 5.4               | 75         | betulin               | 1217 µg/g                           |     |
|                                              | ChCl:lactic acid     | 1:1         | SAE                               | 60        | 5.4               | 105        | betulin               | 1015 µg/g                           |     |
|                                              | ChCl:lactic acid     | 1:1         | SAE                               | 60        | 5.4               | 150        | betulin               | 878 µg/g                            |     |
|                                              | ChCl:lactic acid     | 1:1         | SAE                               | 80        | 5.4               | 75         | betulin               | 1332 µg/g                           |     |
|                                              | ChCl:lactic acid     | 1:1         | SAE                               | 80        | 5.4               | 105        | betulin               | 1788 µg/g                           |     |
|                                              | ChCl:lactic acid     | 1:1         | SAE                               | 80        | 5.4               | 150        | betulin               | 1329 µg/g                           |     |
| <i>Dioscorea nipponica</i> (rhizomes)        | ChCl:malonic acid    | 1:1         | UAE                               | RT        | 30                | 20         | pseudoprotodioscin    | 9710 µg/g                           | 229 |
|                                              | ChCl:malonic acid    | 1:1         | UAE                               | RT        | 30                | 20         | protodioscin          | 29300 µg/g                          |     |
|                                              | ChCl:malonic acid    | 1:1         | UAE                               | RT        | 30                | 20         | protogracillin        | 15860 µg/g                          |     |
|                                              | ChCl:malonic acid    | 1:1         | UAE                               | RT        | 30                | 20         | pseudoprotogracillin  | 3660 µg/g                           |     |
| <i>Salvia officinalis</i> L. (leaves)        | ChCl:lactic acid     | 1:2         | SAE                               | 50        | 10                | 90         | carnosic acid         | 14.43 µg/g                          | 230 |
|                                              | ChCl:lactic acid     | 1:2         | SAE                               | 30        | 10                | 60         | carnosic acid         | 10.68 µg/g                          |     |
|                                              | ChCl:lactic acid     | 1:2         | SAE                               | 70        | 10                | 60         | carnosic acid         | 10.16 µg/g                          |     |
| <i>Ginkgo biloba</i> (leaves)                | ChCl:ascorbic acid   | 1:1         | UAE                               | 70        | 30                | 30         | bilobalide            | 7518 µg/g                           | 102 |
|                                              | ChCl:fructose        | 1:1         | UAE                               | 70        | 30                | 30         | bilobalide            | 6552 µg/g                           |     |
| <i>Xanthoceras sorbifolia</i> Bunge. (husks) | ChCl:glycolic acid   | 1:2         | SAE                               | 60        | 30                | 30         | total saponin content | 60720 µg/g                          | 231 |
| <i>Panax quinquefolius</i> L. (roots)        | ChCl:ethylene glycol | 1:2         | SAE                               | 60        | 20                | 30         | ginsenosides          | 71590 µg/g                          | 232 |
| <i>Trillium govanianum</i> (rhizomes)        | ChCl:lactic acid     | 1:1         | UAE                               | 50        | 0                 | 60         | total saponin content | 114400 µg/g                         | 233 |

<sup>a</sup>UAE, ultrasound-assisted extraction; MAE, microwave-assisted extraction; SAE, stirring-assisted extraction.

Table 7. Extraction of Other Chemicals Using Deep Eutectic Solvents

| biomass                                  | DES                   | molar ratio | method of extraction | temp [°C] | water content [%] | time [min] | extracted compd | yield (calcd on 1 g of dry biomass) | ref |
|------------------------------------------|-----------------------|-------------|----------------------|-----------|-------------------|------------|-----------------|-------------------------------------|-----|
| <i>Ziziphus jujuba</i> Mill. (fruits)    | ChCl:ethylene glycol  | 1:3.75      | SAE                  | 90        | 53                | 120        | polysaccharides | 63600 µg/g                          | 234 |
| <i>Nelumbo nucifera</i> Gaertn. (leaves) | ChCl:ethylene glycol  | 1:3         | SAE                  | 90        | 30                | 180        | polysaccharides | 778900 µg/g                         | 236 |
|                                          | ChCl:ethylene glycol  | 1:3         | MAE                  | —         | 0                 | 6.5        | polysaccharides | 832000 µg/g                         |     |
| <i>Nelumbo nucifera</i> Gaertn. (leaves) | ChCl:propylene glycol | 1:4         | UAE                  | RT        | 30                | 30         | O-nornuciferine | 690 µg/g                            | 241 |
|                                          | ChCl:propylene glycol | 1:4         | UAE                  | RT        | 30                | 30         | nuciferine      | 3340 µg/g                           |     |
| <i>Peumus boldus</i> Mol. (leaves)       | ChCl:levulinic acid   | 1:1         | SAE                  | 60        | 20                | 50         | boldine         | 427 µg/g                            | 242 |
| <i>Phellodendri amurensis</i> (cortex)   | ChCl:citric acid      | 1:2         | UAE                  | 25        | 30                | 30         | berberine       | 10820 µg/g                          | 243 |
|                                          | ChCl:citric acid      | 1:2         | UAE                  | 25        | 30                | 30         | palmatine       | 4740 µg/g                           |     |
| apricot pulp                             | ChCl:tartaric acid    | 2:1         | UAE                  | 30        | 20 (MeOH)         | 10         | β-carotene      | 413 µg/g                            | 244 |

Table 8. Advantage of Using DESs over Organic Solvents in Extraction of Bioactive Compounds from Plant Material

| biomass                                                              | extracted compd         | organic solvent | yield [ $\mu\text{g/g}$ ]<br>(calcd on 1 g of dry biomass) | DES                 | yield [ $\mu\text{g/g}$ ]<br>(calcd on 1 g of dry biomass) | ref |
|----------------------------------------------------------------------|-------------------------|-----------------|------------------------------------------------------------|---------------------|------------------------------------------------------------|-----|
| <i>Mentha piperita</i> (leaves)                                      | chlorogenic acid        | ethanol         | 175.94                                                     | ChCl:malonic acid   | 194.01                                                     | 100 |
| <i>Apocynum ventem</i> L. (leaves)                                   | protocatechuic acid     | methanol        | 284.00                                                     | ChCl:levulinic acid | 418.00                                                     | 90  |
| <i>Ginkgo biloba</i> L. (leaves)                                     | bilobalide              | ethanol         | 5100.00                                                    | ChCl:ascorbic acid  | 7520.00                                                    | 102 |
| <i>Lavandula pedunculata</i> subsp. <i>Lusitanica</i> (aerial parts) | caffeic acid            | methanol        | 81.50                                                      | ChCl:urea           | 248.30                                                     | 257 |
| <i>Olea europaea</i> L. (leaves)                                     | total phenolic content  | ethanol         | 16030.00                                                   | ChCl:acetic acid    | 34610.00                                                   | 88  |
| <i>Carthamus tinctorius</i> L. (flowers)                             | hydroxysafflor yellow A | methanol        | 15540.00                                                   | ChCl:urea           | 22810.00                                                   | 258 |

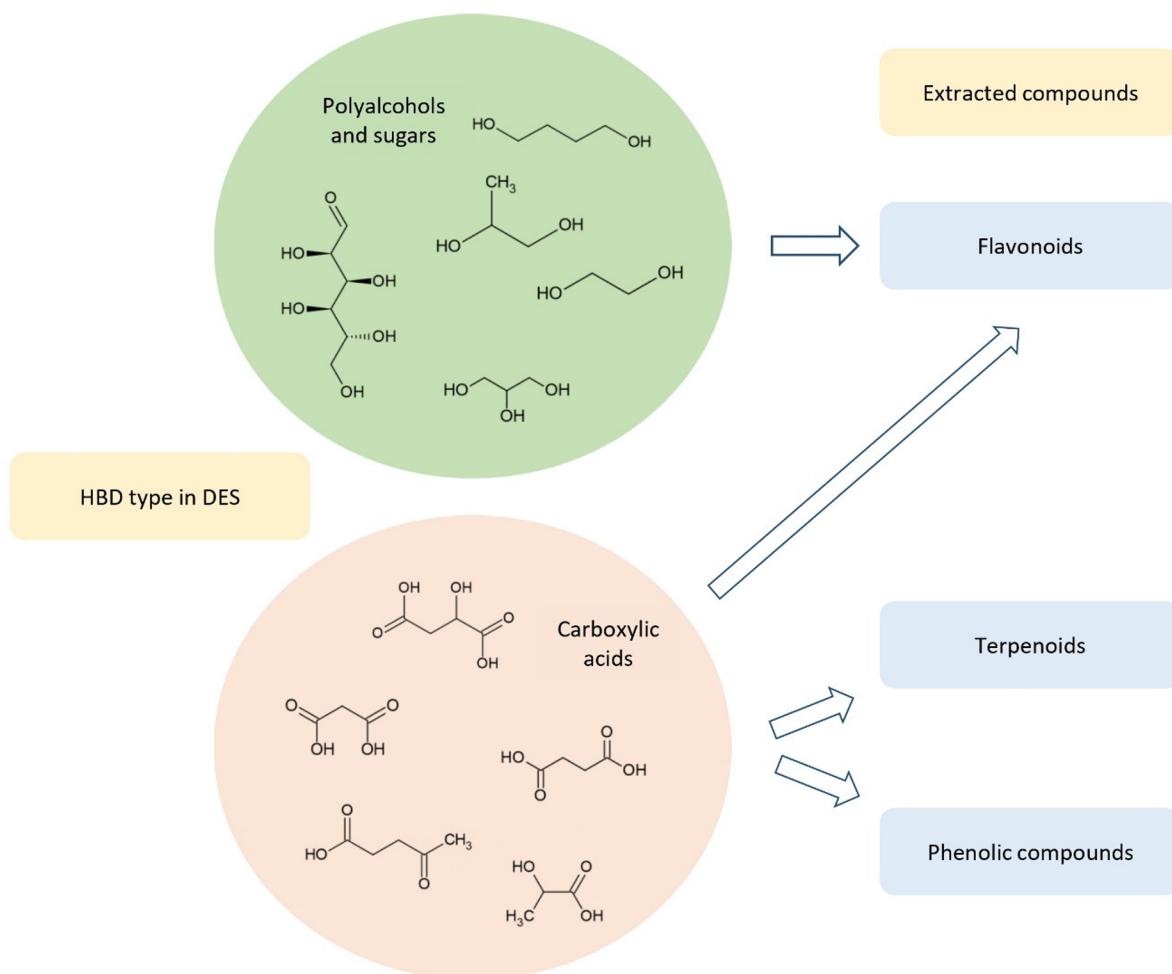


Figure 3. Dependence of HBD in DES and efficiency of extracted metabolites.

saccharides extracted from *Zizyphus jujube* fruits show prebiotic activity, as tested on bacteria.<sup>234</sup> Similar properties were demonstrated for polysaccharides from *Lithocarpus litseifolius* leaves. In addition, these compounds could be applied in diabetes treatment.<sup>235</sup> Polysaccharides extracted from lotus leaves were examined in terms of their antioxidant capacities. Through extraction with DESs, the antioxidant properties of compounds were more intense compared to the extracts isolated with water.<sup>236</sup> Other interesting natural chemicals are alkaloids with potential anti-inflammatory bioactivities. This group of compounds has many possible applications, such as the improvement of immunological

defense and the treatment of cardiovascular and liver diseases.<sup>237–239</sup> Carotenoids are chemicals that are commonly present in edible plants, but due to their hydrophobic nature, the recent literature focuses on applying hydrophobic DESs in their extraction.<sup>240</sup> Table 7 presents a brief review on other chemicals extracted using DESs.<sup>234,236,241–244</sup>

### 3. EFFECT OF TYPE OF DES AND PROCESS CONDITIONS FOR EXTRACTION EFFICIENCY

**3.1. Comparison of DESs and Organic Solvents in the Extraction of Bioactive Plant Ingredients.** Traditional methods of extraction include Soxhlet extraction with solvents

such as ethanol, methanol, and acetone<sup>245</sup> and extraction with the aid of stirring and heating, commonly used together with the assistance of ultrasound or microwaves.<sup>246–249</sup> The application of organic solvents in the extraction processes comes with some disadvantages, such as high flammability, high vapor pressure, and, in some cases, toxicity.<sup>250,251</sup> Additionally, some extracted compounds, e.g., anthocyanins, are prone to degradation at high temperatures. Thus, it is even more difficult to efficiently extract them with organic solvents. Because of that, there is a need for a simple and ecological extraction method under mild conditions.<sup>252</sup> The application of DESs can be an option for solving the above-mentioned problems.<sup>253</sup> In many cases, they are more efficient as extraction media, compared with traditional organic solvents.<sup>30,254</sup> It was shown that higher antioxidant activity was retained by plant extracts obtained using DESs as the extraction media when compared to organic solvents.<sup>255</sup> Apart from a higher extraction efficiency, DESs can be more selective than organic solvents. By changing the HBA and HBD, it is possible to adjust the polarity of a DES to that of the target compound.<sup>256</sup> Additionally, extraction with a DES requires less solvent.<sup>30</sup> A comparison of extraction efficiencies using DESs and organic solvents is presented in Table 8.<sup>88,90,100,102,257,258</sup>

The biggest challenge in extraction processes with DESs is the recovery of the extracted chemicals from the solvent. The low vapor pressure of the DES is an advantage from an ecological point of view, but this makes it impossible to separate the solvent from the extract via distillation, which is a common method in organic solvent extraction. In the latest reports, macroporous resins or solid-phase extraction were applied during the separation of extracted compounds from DESs.<sup>259</sup>

**3.2. Impact of HBA and HBD in DES.** As has been mentioned in previous sections, the impact of the HBD on the extraction efficiency depends on the type of the extracted compound. The extraction of flavonoids can be efficiently performed with DESs that possess HBDs such as polyalcohols and organic acids. In the case of phenolic compounds and terpenoids, higher yields of products are obtained in the presence of DESs composed of organic acids as HBDs<sup>102,108,226</sup> (Figure 3).

This phenomenon is connected with the polarities of DESs and extracted compounds.<sup>260</sup> The interaction of solute and solvent is indicated by the polarity, which in turn can be studied using solvatochromic data. The  $E_TN$  parameter (normalized polarity) and Kamlet–Taft parameters, namely,  $\alpha$  (hydrogen bond donating ability),  $\beta$  (hydrogen bond accepting ability), and  $\pi^*$  (dipolarity/polarizability), give information about intermolecular interactions. It has been shown that, based on  $E_TN$  values of DESs having the same HBD (levulinic acid), a hydrophilic HBA makes the solvent more polar. This has been explained by the stability of the hydrogen bond (chloride anion in hydrophilic choline chloride HBA forms a more stable hydrogen bond with HBD than hydrophobic methanol). It can be assumed that, in DESs based on the same HBD, the character of the HBA controls their dipolarity/polarizability as well as the  $\beta$  parameter. Additionally, DESs with carboxylic acids displayed high  $\alpha$  values. It was also shown that the addition of water to DESs based on choline chloride and polyalcohols decreases the  $\beta$  parameter and increases  $\pi^*$ .<sup>261</sup> The extraction efficiency can be partially predicted by measuring the  $\alpha\beta$  value, which represents the

strength of hydrogen bonding in the solvent. The efficiency of isolation should increase with higher  $\alpha\beta$  values.<sup>262</sup> Many phenolic compounds (e.g., gallic acid and glycyrrhizic acid) are polar, so DESs with higher polarities should be more appropriate for extraction.<sup>263,264</sup> A study presented by Jurić et al. confirmed that DESs containing organic acids with higher polarities compared to polyalcohols and sugars are better extraction solvents for polar metabolites in the plant material.<sup>265</sup> In some cases, extraction with polyalcohol-based DESs is more efficient. For instance, the extraction of phenolic compounds from *Leptospermum scoparium* with DES ChCl:ethylene glycol allowed for better yields of phenolics to be obtained (56.87 mg/g of dry biomass, calculated as equivalents of gallic acid) than those with ChCl:lactic acid (52.51 mg/g of dry biomass) or ChCl:acetic acid (32.49 mg/g).<sup>92</sup> This could be explained by lower viscosities of some DESs with diols as HBDs than with organic acids, which facilitates mass transport during extraction (e.g., the viscosity of ChCl:lactic acid at 25 °C is equal 301.902 mPa·s and that of ChCl:ethylene glycol is equal to 32.045 mPa·s).<sup>92,192</sup> Some hydrophobic DESs, based on fatty acids, also show low viscosities, which improves extraction efficiency.<sup>15</sup> The extraction efficiency also depends on the  $pK_a$  of the HBD and the extracted compound. Metabolites with  $pK_a$  values that are lower than or similar to that of the HBD can form stronger hydrogen bond based interactions with the chloride anion in the HBA, compared to the HBD. This results in a higher extraction efficiency.<sup>226,266</sup> Furthermore, if the extracted compound has more donor groups (carboxylic acid or hydroxyl groups), it can interact with HBAs even more strongly. The formation of hydrogen bonds is connected with solvation enthalpy, which is preferably exothermic. The isolation effectiveness is also driven by the extraction entropy change, which is an effect of breaking the DES structure via the solute. In the solvent structure, a cavity needs to be created to accommodate the solubilized compound. This fact is an explanation for the low extraction efficiencies of larger compounds—more energy is needed to create a cavity. It could be concluded that the isolation effectiveness depends mostly on the hydrogen bond creation between the compound and the chloride atom in the HBA, which is the most significant in extraction of polar chemicals.<sup>266</sup>

The same general rules and exceptions apply to flavonoids.<sup>267</sup> Additionally, many flavonoids are soluble in alkaline solutions, so an extraction with acidic solvents is not preferable.<sup>268</sup>

**3.3. Impact of the Extraction Method and Temperature.** Natural compounds can be extracted using DESs through various methods, including assistance by ultrasound or microwaves or subcritical extraction techniques. These techniques are considered to be more effective than traditional stirring with heating because the plant cell walls can be more easily disrupted, which translates into a more efficient release of bioactive compounds.<sup>269,270</sup> It also decreases the time needed for extraction.<sup>74,153,190</sup> Unfortunately, microwave-assisted extraction can sometimes cause the degradation of sensitive metabolites.<sup>194,271,272</sup>

Considering the influence of the temperature of extraction, most of the processes are performed in the range 40–70 °C. A further increase in the temperature is risky, because some of the compounds, especially phenolics, tend to decompose at high temperatures, which affects their antioxidant properties.<sup>88,194,273</sup> DESs can also react with extracted chemicals

**Table 9. Yields of Extracted Compounds Using DESs, Dependent on Water Content**

| biomass                               | DES              | extracted compd         | water content [%] | yield [mg/g on mass of dry biomass] | ref |
|---------------------------------------|------------------|-------------------------|-------------------|-------------------------------------|-----|
| <i>Glycyrrhiza glabra</i> (roots)     | ChCl:lactic acid | glycyrrhizic acid       | 0                 | 28.00                               | 226 |
|                                       | ChCl:lactic acid | glycyrrhizic acid       | 30                | 50.00                               |     |
| <i>Fagopyrum esculentum</i> (sprouts) | ChCl:oxalic acid | orientin                | 0                 | 0.44                                | 188 |
|                                       | ChCl:oxalic acid | orientin                | 20                | 2.26                                |     |
| <i>Larix decidua</i> (bark)           | ChCl:urea        | total flavonoid content | 25                | 159.00                              | 184 |
|                                       | ChCl:urea        | total flavonoid content | 50                | 305.00                              |     |
|                                       | ChCl:urea        | total flavonoid content | 75                | 275.00                              |     |
| <i>Malus domestica</i> (fruit pomace) | ChCl:lactic acid | total phenolic content  | 10                | 3.90                                | 103 |
|                                       | ChCl:lactic acid | total phenolic content  | 30                | 5.20                                |     |
|                                       | ChCl:lactic acid | total phenolic content  | 50                | 1.20                                |     |

**Table 10. Recovery of Isolated Bioactive Compounds from DESs after Extraction**

| biomass                                              | DES                               | extracted compds          | recovery method                         | recovery rate [%] | ref |
|------------------------------------------------------|-----------------------------------|---------------------------|-----------------------------------------|-------------------|-----|
| <i>Acanthopanax senticosus</i>                       | lactic acid:glycerol              | flavonoids                | resin absorption (D101)                 | 55.76             | 284 |
|                                                      | lactic acid:glycerol              | flavonoids                | resin absorption (AB-8)                 | 77.10             |     |
| <i>Carthamus tinctorius</i> L.<br>citrus fruit peels | ChCl:sucrose                      | carthamin                 | resin absorption (Diaion HP-20)         | 90.00             | 285 |
|                                                      | ChCl:levulinic acid:N-methyl urea | polymethoxylated flavones | back extraction (ethyl acetate)         | 95.87             |     |
| <i>Fagopyrum esculentum</i> Möench                   | ChCl:levulinic acid:N-methyl urea | hesperidin                | back extraction ( <i>n</i> -butanol)    | 86.32             | 188 |
|                                                      | ChCl:triethylene glycol           | orientin                  | SPE (C18 cartridges)                    | 97.81             |     |
|                                                      | ChCl:triethylene glycol           | rutin                     | SPE (C18 cartridges)                    | 98.47             |     |
| <i>Ampelopsis grossedentata</i>                      | ChCl:glycerol                     | flavonoids                | antisolvent (phosphate buffered saline) | 86.75             | 287 |
| <i>Ipomoea batatas</i> L.                            | ChCl:malic acid                   | flavonoids                | resin absorption (AB-8)                 | 85.46             | 289 |
| <i>Citri Reticulatae</i> Pericarpium<br>Viride       | L-proline:urea                    | narirutin                 | resin absorption (SP825)                | 88.00             | 290 |
|                                                      | L-proline:urea                    | hesperidin                | resin absorption (SP825)                | 86.00             |     |

under such conditions, forming undesirable polymeric side products.<sup>274</sup> On the other hand, the higher the temperature, the lower the viscosities of DESs and thus the better the mass transfer. Higher temperatures also enhance the cleavage of bonds between extracted compounds and the plant matrix.<sup>275</sup>

**3.4. Impact of Water Content.** Water content in the extraction media is another crucial element in the isolation of secondary metabolites from plants. Generally, DESs based on choline chloride have high viscosities, which have a negative effect on the extraction yield due to poor mass transfer. This problem can be solved by increasing the temperature of extraction (as was discussed in previous sections) or via the addition of water. In some cases, an addition of 25% (v/v) water to a DES can decrease the viscosity to the level of the water viscosity.<sup>276</sup> Water can also increase the DES polarity, which can facilitate the extraction of some polar compounds, which creates a possibility for enhancing the selectivity of the extraction.<sup>277–279</sup> Because of the high water concentration in the reaction system, the isolation of compounds with weak polarities was reduced, which was shown by Liu et al.: by increasing the water content to beyond 15%, the yield of curcuminoids extracted from *Curcuma longa* L. significantly decreased.<sup>280</sup> On the other hand, too high a water percentage in the solvent can break the hydrogen bond structure of the DES, which leads to the deterioration of its properties and its abilities to extract bioactive compounds from the plant biomass.<sup>273,276,281,282</sup> Apart from hydrogen bond breaking, there is also another possible mechanism that explains this phenomenon. An increase in the water content for the DES ChCl:ethylene glycol to above 30% (v/v) water creates aggregates in which the DES particles are suspended. The

hydrogen bonds between the HBA and HBD compounds are preserved, but the eutectic properties of the solvent are significantly lower.<sup>283</sup> A brief comparison of the extraction efficiencies, dependent on the water content, is presented in Table 9.<sup>103,184,188,226</sup>

#### 4. RECOVERY OF ISOLATED CHEMICALS FROM DESs

The major challenge in the extraction of bioactive chemicals is their recovery from DESs. Because of the negligible vapor pressures of these solvents, it is impossible to separate them from isolated compounds by distillation. There are a few developed methods, which were presented in recent literature, for example, macroporous resin adsorption, solid phase extraction, antisolvent method, and back extraction. The most applied method is adsorption on a macroporous resin, carried out in a packed column or by batch extraction. The recovery rate depends mainly on the type of the resin and its polarity, which should be similar to the polarity of the adsorbate. The most used resins are nonpolar (D-101, HP-20, X-5), middle polar (AB-8), and polar (HPD-600, XAD-7HP). Apart from the resin type, it is important to select the proper eluent, with an optimal desorption capacity.<sup>284,285</sup> Solid phase extraction (SPE) is also one of the most popular methods of bioactive compounds recovery. It requires application of cartridges filled with sorbent, mainly reversed phase or hydrophilic–lipophilic balanced, which interacts noncovalently with the eluted analyte. It is one of the most effective methods, which allows recovery of analytes at a level above 90%.<sup>188</sup> Even though solid phase extraction is considered an efficient method at the laboratory scale, recent findings in sorbent types (e.g., hierarchically porous silica monoliths providing a durable, high

surface area that can be further functionalized with ligands) can open the way to industrial application of that technique.<sup>286</sup> Another recovery method is adding antisolvent to the obtained DES extract, which breaks bonds between the HBA and the HBD. This causes the loss of DES properties and precipitation of the extracted chemicals as the antisolvent water is mostly applied, but also buffers.<sup>287</sup> However, this method is not suitable for all isolated compounds.<sup>288</sup> Back extraction is also a simple method for recovery of chemicals from DESs. It involves re-extraction of analytes with solvents which are immiscible with the DES, but the isolated compounds are soluble in them. The selection of the proper solvent increases the selectivity of re-extraction.<sup>288</sup> Ethyl acetate, *n*-butanol, hexane, and acetone are the solvents most applied; however, they are not considered green chemicals, which makes this method not fully ecological. The economic issue, including the costs of additional solvent, its recovery, and recycling should also be considered. Table 10 presents a brief review on recovery of bioactive compounds from DESs.

## 5. FUTURE PROSPECTS

DESs are considered the solvents of the future that may be used in many fields. They can be applied not only as extraction media but also as drug carriers and adsorbents for harmful metals and organic molecules, H<sub>2</sub>S, and SO<sub>2</sub>, which are common byproducts in various processes. DESs may also be used as medium or catalysts in organic syntheses.<sup>291</sup> There is an impressive number of publications and recently patented processes of extraction of natural products, with different types of DESs and systems containing DESs.<sup>292</sup> The dramatic increase in the number of publications and patents in recent months (67 patent applications within 2022–2023, based on Espacenet) emphasizes the importance of the discussed topic. DESs have been demonstrated to have better extraction properties than many organic solvents, and they seem to be a promising alternative to them, due to the higher yields of extracted bioactive chemicals, preservation of their bioactivity, the mild extraction conditions, and their biodegradability. The proper selection of HBAs and HBDs in DESs allows for a natural, “tailor-made” solvent to be made for the best possible efficiency in the isolation of active compounds. According to the examples presented, the most frequently used solvents are based on organic acids of natural origin, especially lactic acid, which is one of the most suitable HBDs for obtaining high yields for many chemicals. In order to maximize the yields of isolated chemicals, extraction with the assistance of ultrasound or microwaves is recommended. A combination of these techniques with green solvents makes the extraction process more sustainable and consistent with green chemistry rules. Undeniably, studies regarding extractions with DESs are constantly being developed.

This review presented the recent results achieved with DESs, especially solvents based on choline chloride as the HBA. However, there is a growing trend to modify DESs and their properties. Many researchers focus on hydrophobic DESs, which have a great potential for the extraction of less polar compounds, e.g., carotenoids, sulforaphane, and ginkgolic acids.<sup>240,293,294</sup> The other tendency is to prepare ternary DESs and NADESs, composed usually of choline chloride, diol or polyalcohol, and acid, e.g., choline chloride/lactic acid/ethylene glycol or choline chloride/butanediol/citric acid, where the acidity can be tuned by using different amounts of acids.<sup>95,98</sup> In addition, the development of switchable systems

is receiving more attention. With the use of such a system, an efficient and selective separation of compounds with different polarities is possible. For instance, rosmarinic acid and carnosic acid were extracted from rosemary, using a thermo-switchable system composed of a DES and an IL, namely ChCl:levulinic acid and [BMIM]PF<sub>6</sub>. Due to the different polarities of the solvents, the selective extraction of compounds was possible: the IL phase was rich with less polar carnosic acid and, in the DES phase, polar rosmarinic acid was present.<sup>295</sup> Thermo- and pH-switchable DESs are also promising solvents in green extraction. For example, by increasing the pH value, it is possible to create a homogeneous hydrophobic DES–water mixture, and addition of acid after the extraction separates the DES and aqueous phases.<sup>296,297</sup> This is a promising approach to the problem of DES separation after extraction. This problem can also be solved by applying magnetic DESs containing metal oxides or salts, e.g., Fe<sub>3</sub>O<sub>4</sub>, TiO<sub>2</sub>, FeCl<sub>3</sub>, NiCl<sub>2</sub>, and ZnCl<sub>2</sub>. These solvents can be separated from the aqueous solution by using a magnetic field. Furthermore, there is evidence from the literature that magnetic DESs are more effective extraction media than traditional DESs.<sup>298,299</sup> From the separation of the solute after extraction point of view, deep eutectic solvent molecularly imprinted polymers (DES-MMIPs) have great potential. For example, MMIPs with choline chloride/cafeic acid/formic acid used as functional monomers were obtained and successfully used in the extraction and determination of hormones from lotion.<sup>300</sup> When new deep eutectic systems are designed for extraction, their price must be taken into account. Classic DESs are valued for their properties but also for the simple way of obtaining them and their relatively low price. Modern systems require more work and are more expensive. In the final calculation, however, the entire extraction process, the entire economy, the amount of waste, and, above all, the yield of the isolated, pure product must be taken into account.

The most important difficulties in the application of DESs in industrial extraction processes are the high viscosities of many of them, as well as the separation of the solute after extraction. Design of DESs with lower viscosities by selecting new, biodegradable, natural, and cheap HBAs and HBDs, and mixing them in appropriate ratios, seems to be one of the challenges on the way to the industrial use of these solvents. The viscosity problem can also be solved by the addition of water to the extraction system or an increase of temperature. The amount of added water should be thoroughly examined, in order to maintain the properties of DESs. According to the literature, usually addition of up to 30% of water is safe, but there are also publications where even 50% of water was used, especially in ternary systems.<sup>95</sup> Another issue is an efficient separation of the extracted compounds from the solvents, which is crucial in the application of extracts in pharmaceuticals, cosmetics, or foods. As previously mentioned, application of switchable systems, ternary systems, or magnetic DESs can be a solution for that problem. However, a simple, more economical and efficient method of solute recovery and solvent recycling should be elaborated. Finally, even though most DESs are considered biocompatible, nontoxic, and environmentally friendly, their application in the extraction of cosmetic, food, and pharmaceutical ingredients needs an individual, thorough safety examination.

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## Notes

The authors declare no competing financial interest.

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