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1     **Impact of conventional and sustainable solvents on the yield, selectivity and recovery of**  
2                                   **curcuminoids from turmeric**

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**20 ABSTRACT:**

21           Extraction of pharmaceutically important curcuminoid platform molecules has been  
22 achieved from turmeric with ultrasound-assisted greener solvent extraction, demonstrating  
23 excellent extraction performance and product recovery. Extraction of curcuminoids from turmeric  
24 was undertaken with both conventional and potentially bio-based solvents. Sustainable solvents,  
25 namely, ethyl acetate, ethanol, Cyrene and deep eutectic solvent (DES-B5, 1:6 ChCl:1,4-  
26 butanediol) demonstrated high extraction yields of curcuminoids, including  $24.36 \pm 3.10$  mg/g,  
27  $25.30 \pm 4.58$  mg/g,  $23.51 \pm 2.56$  mg/g and  $27.40 \pm 3.80$  mg/g of curcumin, respectively. In contrast,  
28 curcumin extracted in lower polarity solvents such as hexane, toluene and tetramethyloxolane  
29 (TMO) were low at less than 7.0 mg/g. DES-B5 with 10% water extracted the greatest yield of  
30 curcumin ( $46.70 \pm 0.55$  mg/g), bisdemethoxycurcumin ( $46.14 \pm 0.82$  mg/g) and  
31 demethoxycurcumin ( $10.63 \pm 0.35$  mg/g), followed by a simple and low energy product recovery  
32 method through the addition of water and precipitation. COSMOtherm calculations suggested that  
33 extraction efficiency was related to solvent interactions with the cell walls of the biomass, rather  
34 than the solubility of the curcuminoids. In addition, application of ultrasound in extraction in  
35 combination with DES-B5 enabled the strong destruction of plant matrix that was confirmed by  
36 scanning electron microscopy (SEM). The sustainability, efficiency and toxicity of proposed  
37 extraction methodologies were evaluated through the CHEM21 green metrics toolkit. The methods  
38 utilising ethanol, ethyl acetate and Cyrene in this work demonstrate a significant improvement  
39 over those previously published by 3 to 10 times of process mass intensity (PMI) total, while DES-  
40 B5 also performed well under the green metric assessment. Because of its high yields, bio-based  
41 solvent, low toxicity, being inexpensive and readily available, DES-B5 with 10% water is  
42 recommended as the greenest solvent for curcuminoid extraction under ultra-sonication.

43 **KEYWORDS:** Curcuminoids; *Curcuma longa*; Cyrene; Deep eutectic solvents; ultrasound;  
44 tetramethyloxolane (TMO).

45

## 46 **INTRODUCTION**

47 Turmeric (*Curcuma longa*) is an important plant in a family of ginger and can be found  
48 across Asia including India, Indonesia and Thailand. It is used widely as an ingredient of food,  
49 herbal medicine and in natural dyes.<sup>1</sup> There are three important components in the turmeric  
50 rhizome that are collectively known as “curcuminoids”: curcumin (**1**), bisdemethoxycurcumin (**2**)  
51 and demethoxycurcumin (**3**), as shown in Figure 1. Curcumin especially is well known as a yellow  
52 natural product with bioactive properties including antioxidant, anti-inflammatory, anticancer,  
53 anti-diabetic and anti-microbial activities.<sup>2-4</sup> Therefore, it is an attractive platform molecule for the  
54 development of new drug candidates by the pharmaceutical industry. Unfortunately, curcuminoids  
55 are low-polarity organic compounds that are insoluble in water.<sup>5</sup> Furthermore, they are thermally  
56 liable phenolic compounds that also degrade in strong light.<sup>6</sup> As such, the use of conventional  
57 organic solvents under mild extraction conditions are necessary for further application of  
58 curcuminoids. Nowadays, curcuminoids are often extracted with conventional solvents, namely,  
59 dichloromethane, methanol or acetone.<sup>7,8</sup> One possible methodology to enhance safety and  
60 efficiency for curcuminoid extraction is an application of green solvents, for instance, bio-based  
61 solvents (from starch, wood or vegetable) or environmentally friendly petroleum-based  
62 solvents.<sup>9,10</sup> The utilization of green solvents instead of hazardous or highly hazardous solvents  
63 such as benzene, toluene, diethyl ether and halogenated solvents can be less harmful to human  
64 health and the environment. Bio-based Cyrene is alternative green solvent with excellent  
65 properties, namely, low toxicity, non-mutagenicity and biodegradability.<sup>11</sup> It has been successfully

66 utilised instead of conventional dipolar aprotic solvents such as *N,N'*-dimethylformamide (DMF)  
67 and *N*-methyl pyrrolidinone (NMP). However, Cyrene offers a higher boiling point (203 °C) and  
68 a higher viscosity (1.25 g/mL) that can limit its application in extraction. Tetramethyloxolane  
69 (TMO) is non-peroxide forming ether that derives from potentially renewable feedstocks.<sup>12</sup> It is  
70 alternative green solvent to toluene, representing similar properties such as melting point (-95 °C),  
71 density (0.802 g/mL) and boiling point (112 °C). TMO has the potential to be reaction solvent in  
72 esterifications, amidations and Grignard reactions.<sup>12</sup>

73 In addition, deep eutectic solvents (DESs) have been developed as alternative green  
74 solvents which are well known as one class of ionic liquids (IL), representing excellent properties  
75 such as low price, potential biodegradability, low-toxicity, low-volatility, non-flammability and  
76 are stable at high temperature.<sup>13,14</sup> Generally, DESs are synthesised from two components  
77 including a hydrogen bond donor (HBD, *e.g.* ethylene glycol, glycerol and organic acid) and a  
78 hydrogen bond acceptor (HBA, *e.g.* quaternary ammonium salts) via hydrogen bond formation. In  
79 2020, Altunay *et al.* studied a microextraction of curcumin from spiked foodstuff samples with  
80 deep eutectic solvents.<sup>15</sup> The highest percent recovery of curcumin in spiked food samples was  
81 observed in DES that was prepared from betaine hydrochloride and glycerol at 1:3 ratio. However,  
82 the extraction was studied only in small scale for analytical chemistry. In 2021, Degot *et al.*  
83 extracted curcuminoids from turmeric rhizome with ethanol and food additives (triacetin and  
84 diacetin).<sup>16</sup> The results showed that the addition of triacetin provided advance extraction power.  
85 As a result, the use of combination solvent for curcuminoid extraction can increase the extraction  
86 efficiency. Therefore, from the previous reports, the efficient extraction of curcuminoids in greener  
87 solvents, namely, Cyrene, TMO and DESs remains of interest.

88           Herein, this work aimed to investigate curcuminoid extraction using conventional and  
89 alternative green solvents to develop sustainable methods for natural product extraction.  
90 Ultrasound-assisted extraction (UAE) was utilized as an energy efficient green technology to  
91 rupture the cell wall of the plant matrix to enhance the extraction process. Furthermore, a series of  
92 choline chloride based DESs were synthesised and used in parallel with conventional and other  
93 green solvents for curcuminoid extraction. The curcuminoids were evaluated by RP-HPLC  
94 analysis. Moreover, computational analysis using Conductor-like Screening Model for Realistic  
95 Solvents (COSMO-RS) was conducted with selected solvents to rationalize the experimental  
96 results.

97

## 98 **EXPERIMENTAL SECTION**

### 99 **Materials**

100           Acetonitrile (HPLC grade, Merck, Germany), DMF, ethanol (HPLC grade), ethyl acetate,  
101 hexane, methanol (HPLC grade), glycerol, tetrahydrofuran (THF), toluene and common reagents  
102 were obtained from local suppliers. Cyrene from renewable cellulose was supported by Circa  
103 company (>99.0%, Australia). 2-Methyltetrahydrofuran (2-MeTHF) (purity >99.5%, bio-  
104 renewable source) was purchased from Sigma Aldrich company, USA. TMO was synthesised in  
105 the laboratory according to the previous procedure.<sup>12</sup> Choline chloride (ChCl) (purity >98.0%),  
106 ethylene glycol (>99.5%) and 1,4-butanediol (99.0%) were obtained from Tokyo Chemical  
107 Industry, Japan.

108

### 109 **Plant material**

110 Turmeric powder from *Curcuma longa* rhizomes was purchased from a local market in  
111 Khon Kaen province, Thailand. The dried powder was stored in a sealed dark bag at ambient  
112 temperature protected from the light and humid exposure.

113

#### 114 **Preparation of DES**

115 Choline chloride (ChCl) and a hydrogen bond donor (HBD) of either ethylene glycol, 1,4-  
116 butanediol or glycerol were combined to prepare DESs via hydrogen bond formation. The choline  
117 chloride based DESs were prepared by mixing ChCl and each HBD in 250 mL beaker and heated  
118 at 80 °C for 30 minutes with stirring until a homogenous solution was formed. The component  
119 ratio of choline chloride based DESs are presented in Table 1. Even though most DESs were  
120 synthesised easily at 80 °C, DES-B1 was reheated for five times to form stable DES at room  
121 temperature.<sup>17</sup> An attempt to synthesise betaine hydrochloride-based DESs was not successful.

122

#### 123 **Extraction of curcuminoids from *Curcuma longa***

124 Curcuminoids were extracted from 5 g of turmeric powder in 15 mL of solvent, including  
125 hexane, ethyl acetate, DMF, ethanol, toluene, Cyrene, 2-MeTHF and TMO under ultra-sonication  
126 (35 kHz, RK 103 H, Bandelin, Germany) for two hours at ambient temperature. Afterward, the  
127 crude extracts were filtered using filter paper, and the dried crude extracts were obtained using  
128 rotary evaporator (Buchi R-300, Switzerland). The dried crude extracts were transferred, and the  
129 volume adjusted in a 25 mL volumetric flask by addition of HPLC grade methanol. Finally,  
130 curcuminoids in crude extracts were evaluated using HPLC equipment (Supporting information,  
131 Scheme S1). The extractions were carried out in triplicate. In the case of deep eutectic solvents,

132 curcuminoids were also extracted in parallel with the other solvents. However, a centrifugation  
133 was applied instead of filtration due to high viscosity of DESs.

$$134 \quad \text{Selectivity of total curcuminoids} = \frac{\text{total curcuminoids (mg)}}{\text{dried crude extract (mg)}} \times 100 \quad (1)$$

$$135 \quad \text{Selectivity of each curcuminoid} = \frac{\text{curcuminoid (mg)}}{\text{total curcuminoids (mg)}} \times 100 \quad (2)$$

### 136 **HPLC Analysis**

137 Curcuminoids were measured by RP-HPLC following a previous report with some  
138 modification.<sup>18</sup> The quantity of curcuminoids was evaluated by Agilent 1200 series HPLC system  
139 (Agilent, San Jose, CA, USA). The separation was carried out using acetonitrile (A) and 0.1 M  
140 ammonium acetate buffer pH 3.50 (B) as mobile phases with a gradient elution program. The  
141 initial composition of mobile phase was 50:50 v/v. The linear gradient was applied to A-B (30:70,  
142 v/v) in 8.0 min. Then, the composition of mobile phase was changed to 100% of A in 4.0 min. The  
143 C18 column (4.6 × 150 mm × 5 μm, Agilent, USA) was utilized for separation at ambient  
144 temperature. The injection volume was 10 μL with flow rate of mobile phase 1 mL/min and the  
145 target curcuminoids were detected at 425 nm. The calibration curves of standards of curcumin,  
146 bisdemethoxycurcumin and demethoxycurcumin were established from 2-150 ppm in order to  
147 identify and determine the quantity of curcuminoid content (Supporting information, Figure S1).

148

### 149 **Isolation of curcuminoids from DES**

150 The addition of water induced precipitation of curcuminoids in the crude DES extract. The  
151 appropriate conditions were studied by varying the amount of water in 1 mL of crude DES extract.  
152 The optimised conditions appeared to be three-fold of water. The solid curcuminoid precipitate  
153 appeared after the addition of water. Afterward, the solids were filtered, washed with water and



154 dried in an oven at 40 °C. Subsequently, the curcuminoids were kept in a desiccator until a stable  
155 mass was observed.

156

### 157 **Conductor-like Screening Model for Real Solvents (COSMO-RS)**

158 ArgusLab (version 4.0.1, Mark Thompson and Planaria Software LLC, 2004, Seattle, WA,  
159 USA) was used to obtain approximate atomic coordinates of compounds. The conformations of  
160 the curcuminoids were calculated with COSMOconfX (version 4.0; COSMOlogic GmbH & Co.  
161 KG, Leverkusen, Germany, 2015). COSMOthermX (version C30\_1705; COSMOlogic GmbH &  
162 Co. KG, 2017, TZVP basis set level) was used to provide molecular surface charges and execute  
163 the virtual experiments.

164

## 165 **RESULTS AND DISCUSSION**

### 166 **Extraction of Curcuminoids from *Curcuma longa***

167 To seek the best solvent for curcuminoid extraction, comparative studies between  
168 conventional and green solvents were investigated. Curcuminoids including curcumin,  
169 bisdemethoxycurcumin and demethoxycurcumin were extracted from turmeric rhizome powder  
170 using conventional solvents (hexane, DMF, toluene, ethyl acetate, ethanol and THF) and  
171 alternative green solvents (2-MeTHF, TMO and Cyrene). The selected solvents exhibit a range of  
172 properties, as shown in Table 2. Curcuminoids are thermally labile and as such UAE was utilised  
173 to enhance the extraction yield and avoid the higher temperatures that may lead to degradation.<sup>19</sup>  
174 The quantity of extracted curcuminoids were evaluated by RP-HPLC with UV-VIS detection at  
175 425 nm. The results demonstrated that the extract was predominantly curcumin and  
176 bisdemethoxycurcumin in most solvents, with small amounts of demethoxycurcumin also

177 observed. Curcumin extracted in lower polarity solvents such as hexane, toluene and TMO was  
178 less than 7.0 mg/g, whereas in the polar solvents including ethanol, ethyl acetate and Cyrene  
179 excellent extraction yields were exhibited of  $24.36 \pm 3.10$  mg/g,  $25.30 \pm 4.58$  mg/g and  $23.51 \pm$   
180  $2.56$  mg/g, respectively (Figure 2). These polar solvents also demonstrated excellent extraction  
181 yields of bisdemethoxycurcumin and demethoxycurcumin. The highest yield of  
182 bisdemethoxycurcumin was  $25.57 \pm 3.45$  mg/g, as observed in ethanol. Ethyl acetate and Cyrene  
183 exhibited the similar bisdemethoxycurcumin extraction yields of  $23.54 \pm 2.64$  mg/g and  $23.37 \pm$   
184  $2.44$  mg/g, respectively. Ethanol also gave the highest extraction yield of demethoxycurcumin at  
185  $6.10 \pm 0.82$  mg/g. The extraction yields of demethoxycurcumin from ethyl acetate and Cyrene  
186 were  $5.34 \pm 0.87$  mg/g and  $5.97 \pm 0.71$  mg/g respectively. However, some polar solvents, including  
187 THF ( $15.17 \pm 2.08$  mg/g), 2-MeTHF ( $13.80 \pm 3.90$  mg/g) and DMF ( $14.43 \pm 4.46$  mg/g) only led  
188 to low to moderate extraction yields of curcumin. These solvents also provided low extraction  
189 yields of bisdemethoxycurcumin and demethoxycurcumin.

190 Kumboonma *et al.* investigated the recovery of curcuminoids by the conventional  
191 methodology of soaking turmeric rhizome powder in three sequential extractions of  
192 dichloromethane at room temperature. The isolated curcumin, bisdemethoxycurcumin and  
193 demethoxycurcumin was found to be 33.33 mg/g, 1.66 mg/g and 0.083 mg/g, respectively after  
194 column chromatography.<sup>21</sup> Accordingly, the best three solvents in this current work (ethanol, ethyl  
195 acetate and Cyrene) provided a comparable extraction yields of curcumin. Interestingly, the  
196 extraction yields of bisdemethoxycurcumin and demethoxycurcumin from the ethanol extract were  
197 73 and 15 times greater respectively than that of the dichloromethane extract. Even though  
198 excellent extraction yields of curcuminoids were obtained with ethanol, ethyl acetate and Cyrene,  
199 these solvents present some minor health and safety hazards. As an alternative, DESs were

200 designed and synthesised from natural sources to further investigate the extraction, due to their  
201 attractive properties such as low toxic, reusable, low cost, non-flammable, and biodegradable  
202 properties. Therefore, several choline chloride-based DESs were synthesised using ethylene  
203 glycol, 1,4-butanediol and glycerol and applied to the curcuminoid extraction from turmeric. The  
204 selected chemicals for synthesis of DESs were considered and chosen from their safety, low  
205 toxicity and natural source.<sup>13,38</sup> In addition, ChCl-based DESs increased the flavonoid extraction  
206 capacity due to weak acidity from hydroxy groups on flavonoids which related to the structure of  
207 curcuminoids.<sup>22</sup> Hence, the ChCl-based DESs were selected in this work. The ratio of hydrogen  
208 bond acceptor (HBA) and hydrogen bond donor (HBD) was varied from 1:2 to 1:6 HBA:HBD.

209         The method of curcuminoid extraction with DESs was partially modified by application of  
210 centrifugation on account of the high viscosity of DESs. The extraction results indicated that both  
211 the ethylene glycol and glycerol based DESs tended to decrease the extraction yield when the ratio  
212 of HBD was increased. On the other hand, 1,4-butanediol-based DESs exhibited increased  
213 extraction yields with the increased ratio of HBD as shown in Figure 3. A poor extraction yield  
214 was observed in all glycerol-based DESs, this was likely due to the high viscosity of the solvent  
215 hindering the extraction and preventing mass transfer of the target molecules from the plant  
216 matrix.<sup>23</sup> Among all DESs, DES-B5 (1 part choline chloride, 6 parts 1,4-butanediol) demonstrated  
217 the best yield of curcumin ( $27.40 \pm 3.80$  mg/g), bisdemethoxycurcumin ( $23.24 \pm 0.61$  mg/g) and  
218 demethoxycurcumin ( $5.22 \pm 0.61$  mg/g). DES-B5 possessed the lowest viscosity among 1,4-  
219 butanediol based series because of the increasing of HBD proportion that allowed mass transfer  
220 process.<sup>23,24</sup>

221

## 222 **Optimization of the Curcuminoid Extraction Conditions**

223 Due to the highest extraction efficiency, DES-B5 was further selected as the DESs for  
224 optimisation of the extraction. The greatest curcuminoid extraction increased with solvent volume  
225 until a ratio of 1:15 g/mL. After which, higher quantities of DESs slightly decreased the  
226 curcuminoid yield, as shown in Figure 4 (a). Therefore, the ratio with the highest extraction yield  
227 (1:15 g/mL) was selected for further optimisation. The water content of the DESs was further  
228 investigated with the addition of 0% to 40% v/v. The extraction results indicated that 10% water  
229 content afforded advance extraction performance of curcuminoids: curcumin ( $43.35 \pm 1.49$  mg/g),  
230 bisdemethoxycurcumin ( $42.23 \pm 0.33$  mg/g) and demethoxycurcumin ( $9.62 \pm 0.50$  mg/g) as shown  
231 in Figure 4 (b). A likely explanation for the beneficial effect of adding a small quantity of water  
232 (10% v/v) is the reduction in viscosity of the DES, and it might affect to swell of plant matrix and  
233 solvent penetration, therefore benefiting mass transfer during the extraction process.<sup>25-29</sup>  
234 Moreover, a water content of Cyrene was also studied, however the extraction yield was not  
235 enhanced by the addition of water (Figure S3, supporting information).

236 The total curcuminoids extracted with each solvent were calculated as the sum of curcumin,  
237 bisdemethoxycurcumin and demethoxycurcumin based on HPLC as shown in Table 3. Ethanol,  
238 ethyl acetate, Cyrene and DES-B5 (with 10% water) afforded the highest total curcuminoids with  
239 56.03 mg/g, 54.17 mg/g, 52.85 mg/g and 55.86 mg/g, respectively. The results indicated that the  
240 alternative green solvents, namely, Cyrene and DES-B5 exhibited extraction performance like  
241 ethanol and ethyl acetate. The results suggested that the extraction of curcuminoids was not only  
242 influenced by polarity and viscosity, but it might be affected by several factors such as penetration  
243 of solvent and encapsulation of target molecule from the plant matrix.<sup>30</sup>

244

245 **Recovery of curcuminoids from Cyrene and DESs Extracts**

246 To isolate the curcuminoids from the crude extracts, vacuum evaporation was applied to  
247 most of the conventional and green solvents. However, the high boiling points of Cyrene and DES-  
248 B5 make vacuum evaporation an unfeasible method for drying the crude extracts. Cyrene is known  
249 to form a geminal diol upon the addition of water, and the intermolecular hydrogen bonding  
250 observed in DES is disrupted by the addition of water.<sup>31-33</sup> Therefore, the addition of water was  
251 used to induce precipitation of curcuminoids from the crude Cyrene and DES extracts. The solid  
252 curcuminoid precipitate appeared immediately after the addition of water. The precipitation  
253 process was left for 1 day to obtain the complete product. This phenomenon of forming a geminal  
254 diol reduces curcuminoid solubility and permits isolation of the crude extract without the direct  
255 energy consumption required by distillation. Afterward, the solids were filtered, washed with  
256 water, and dried in an oven at 40 °C. Subsequently, the curcuminoids were kept in a desiccator  
257 until a stable mass was observed. The absence of Cyrene in the dried crude extract was confirmed  
258 by proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectroscopy. The dried crude extracts of all  
259 solvents were represented in Table 3. The results indicated that the maximum dried crude extract  
260 was obtained from Cyrene with 124.33 ± 5.13 mg/g. Slightly lower yields were observed in ethyl  
261 acetate, ethanol, DES-B5 and DMF, respectively. Lower dried crude yields around 75.0-90.0 mg/g  
262 were obtained from TMO, THF and 2-MeTHF, while low-polar solvents, including hexane and  
263 toluene, exhibited dry crude extracts lower than 65.0 mg/g. The large mass of the dried crude  
264 extracts suggested that non-curcuminoid compounds were also extracted from turmeric powder in  
265 all solvents. The non-curcuminoids in the crude extract were presumed to be derived from other  
266 organic compounds or pigments found in turmeric.

267

### 268 **Comparison of curcuminoid selectivity**

269 The selectivity of curcuminoid extraction from DES-B5 (relative to the crude extract) was  
270 56%, exhibiting the highest selectivity among all solvents in this work. The selectivity of  
271 curcuminoid extraction was high for ethanol, ethyl acetate, Cyrene and 2-MeTHF at 49%, 46%,  
272 43% and 41%, respectively. A lower selectivity for curcuminoids (10-39%) was observed from  
273 THF, DMF, TMO, toluene and hexane. Most solvents exhibited more than 50% non-curcuminoids  
274 in dried crude extracts. A selectivity of each curcuminoid between the three curcuminoids was also  
275 calculated as shown in Figure 5. As a result, toluene exhibited the highest selectivity of curcumin  
276 at 55%, and DES-B5 provided a higher selectivity towards curcumin than that of most  
277 conventional and other green solvents. TMO was highly selective towards bisdemethoxycurcumin.  
278 A lone pair of ethereal oxygen of TMO could interact with a proton of phenolic compound via  
279 weak hydrogen bond proposed by Byrne *et al.*<sup>34</sup> Therefore, TMO with four bulky methyl groups  
280 was able to interact with hydroxy group of bisdemethoxycurcumin, which has the lowest steric  
281 hindrance of the three curcuminoids. For this reason, TMO specifically interacts with  
282 bisdemethoxycurcumin.

283

#### 284 **Exploration of Dissolving Mechanism Using COSMO-RS and Solubility Test**

285 The different performance of solvents in curcuminoid extraction was evaluated by  
286 COSMO-RS, calculating the possible interactions of each solvent with the target curcuminoids.  
287 Ultimately there is no consistent polarity profile or physical property of the solvents that correlates  
288 to extraction performance. The results indicate that the interactions between solvent and the  
289 biomass matrix, such as the hydrogen bonding between the structure of the cell wall and DES is  
290 critically important.<sup>24</sup> A solubility test was conducted to confirm if the curcuminoid extraction  
291 yield was strongly influenced by solubility (Table 3) and the major curcuminoid, curcumin, was

292 selected for this test. The results indicated that both THF and DMF had excellent curcumin  
293 solubility, at greater than 300 mg/mL. Curcumin solubility was also good for Cyrene and 2-  
294 MeTHF at 83.23 mg/mL and 71.79 mg/mL, respectively. A lower curcumin solubility was  
295 observed in ethyl acetate and ethanol of 26.49 mg/mL and 7.19 mg/mL, respectively, despite  
296 demonstrating high yields of extraction. The experimental results of curcumin solubility were  
297 consistent with the predicted solubility of curcumin from COSMO-RS that confirmed DMF and  
298 THF as the best solvent for curcumin solubility. These results demonstrate that the solubility of  
299 curcuminoids does not correlate with the extraction yield, and the expected increase in solubility  
300 with the gradual increase in temperature during ultra-sonication from room temperature to  $55 \pm 2$   
301 °C would further diminish any solubility limit on the extraction of curcuminoids from the plant  
302 matrix.

303

#### 304 **Destruction and Dissolution of the Plant Matrix in UAE**

305 To investigate the effect of UAE on the plant matrix, a morphology of plant residues was  
306 examined by scanning electron microscopy (SEM). The plant residues before and after extraction  
307 with Cyrene and DES-B5 were studied as shown in Figure 6. The results indicated that the  
308 morphology of turmeric rhizomes cell walls before extraction were intact layers. Post extraction  
309 with Cyrene resulted in the partially breakdown plant cell walls leading to the release of target  
310 molecule to the solvent. However, in the case of extraction with DES-B5 this effect was further  
311 enhanced leading to the rupturing of cell walls. SEM results from Cyrene and DES-B5 were  
312 consistent with the extraction yields. This leads to a proposed mechanism for extraction, where the  
313 higher extraction performance relates to the strong hydrogen bonding between DES-B5 and  
314 biomass leading to the destruction of plant cell walls and dissolution of curcuminoids which is

315 consistent with the literature.<sup>35</sup> Several hydroxy groups on plant cell wall (cellulose, and  
316 hemicellulose) could form hydrogen bond interactions with DES-B5 as shown in Figure 7.  
317 Therefore, target molecules could be released and washed out once hydrogen-bond interactions  
318 between cellulose and DES-B5 with application of UAE rupture cell walls.

319

## 320 **CHEM21 Green Metrics Toolkit Assessment**

### 321 **Safety and Toxicity of Solvent Extraction**

322 In terms of solvent toxicity, the CHEM21 solvent selection guidelines was applied to  
323 suggest the safest solvents for curcuminoid extraction.<sup>36</sup> According to their hazards, solvents were  
324 categorised as either highly hazardous, hazardous, problematic or preferred. Classification of  
325 safety, health and environmental hazards has been made on a 1 (low) to 10 (high) scoring system.  
326 Dichloromethane was considered by using CHEM21 solvent selection guide as hazardous. Ethyl  
327 acetate and ethanol were categorised as preferred solvents, while Cyrene was classified as  
328 problematic due to its high boiling point (Table 4). Despite this, the bio-based Cyrene exhibited  
329 lower safety and health issues than that of ethyl acetate and ethanol. Moreover, it represents some  
330 excellent properties, including, non-mutagenicity, no acute oral toxicity ( $LD_{50} > 2000$  mg/kg, the  
331 highest concentration tested), biodegradability (99% in 14 days) and low ecotoxicity.<sup>38</sup> The issue  
332 of the high boiling point of Cyrene was avoided by precipitation of the extract. Furthermore, the  
333 mixture of Cyrene and water offered an advantage as effective solvent extraction in previous  
334 work.<sup>38</sup> Although isolation of the product was not an energy intensive process, the recovery and  
335 reuse of Cyrene after addition of water was challenging.

336 Sustainable DESs were not classified in CHEM21 green metrics toolkits. However, the  
337 individual components can be assessed. Ethylene glycol and glycerol are categorised as preferred



338 and problematic solvents respectively, the major difference being their boiling point. The  
339 greenness of 1,4-butanediol was calculated according to the CHEM21 toolkit methodology as  
340 problematic, despite minimal safety, health and environmental hazards because of its low  
341 volatility. Choline chloride is considered safe, biodegradable, and inexpensive, which was  
342 frequently used as a favourable HBA in the synthesis of DESs. As the safety and toxicity profiles  
343 of individual components were encouraging, and as such it was presumed the toxicity of choline  
344 chloride based DESs was also low. Such statements are backed up toxicity measurements with the  
345 human HEK-293 cell lines, however, a comprehensive toxicity testing of DESs is needed prior use  
346 at scale or application in industry.<sup>39</sup>

347

#### 348 **Evaluation and Comparison of Solvent Extraction Power Using CHEM21**

349 The CHEM 21 green metrics toolkit was also used to assess an efficiency of curcuminoid  
350 extraction processes and was compared with two previous published sustainable  
351 methodologies.<sup>16,40</sup> The green metric selected for the assessment of the extractions was process  
352 mass intensity (PMI) (Table 5), the low PMI value referred to an effective method for extraction  
353 process. Ethanol extract in this work offered the lowest PMI total with 60.1 g/g, while ethyl acetate  
354 and Cyrene exhibited higher PMI with 68.4 g/g and 89.5 g/g, respectively. Although ethyl acetate  
355 offered the higher curcuminoid yield than ethanol, the PMI of ethyl acetate was greater than that  
356 of ethanol because of solvent density. Degot *et al.* extracted curcuminoids from turmeric powder  
357 using a mixture of triacetin (TriA)/Ethanol/H<sub>2</sub>O (36/24/40% w/w) and pure ethanol under stirring  
358 at room temperature for 1 h, and the quantification of curcuminoids was evaluated by HPLC  
359 analysis.<sup>16</sup> Very recently, Huber *et al.* also extracted curcuminoids from turmeric rhizomes with  
360 NADES-based surfactant-free microemulsions (NADES-SFME, ChCl + Lactic acid/Ethanol/TriA

361 35/27.5/37.5% w/w) under the similar condition with Degot *et al.*<sup>40</sup> PMI calculations of two  
362 previously published extraction methods<sup>16,40</sup> with pure ethanol, a mixture of TriA/Ethanol/H<sub>2</sub>O  
363 (36/24/40% w/w) and ChCl + Lactic acid/Ethanol/TriA (35/27.5/37.5% w/w), expressed higher  
364 total PMI with 757.6 g/g, 327.2 g/g and 505.9 g/g, respectively. Therefore, the methods utilising  
365 ethanol, ethyl acetate and Cyrene in this work demonstrate a significant improvement over  
366 previously published works. The PMI of the extraction process using DES-B5 was 71.9 g/g and  
367 demonstrated a higher value than that of ethanol and ethyl acetate, but lower than that of Cyrene.  
368 Moreover, the PMI of the traditional literature method employing dichloromethane for  
369 curcuminoid extraction was also estimated based on the quantity of curcuminoids recovered after  
370 column chromatography.<sup>21</sup> The PMI total of dichloromethane was calculated in this work using  
371 only the amount of starting material, solvent for extraction and the obtained curcuminoids from  
372 the previous work.<sup>21</sup> PMI total of dichloromethane as 218.1 g/g showed higher number than that  
373 of sustainable solvents in this work, namely ethanol, ethyl acetate, Cyrene and DES-B5. Even  
374 though the materials used for column chromatography not accounted for, this indirect comparison  
375 guided us that the low PMI of sustainable solvents (ethanol, ethyl acetate, Cyrene and DES-B5)  
376 offered the potential for substitution the highly hazardous solvent, dichloromethane. These results  
377 demonstrate that the proposed method of curcuminoid extraction with application of ultra-  
378 sonication significantly improved a lower input mass per gram for curcuminoid extraction.  
379 However, there is no universal solvent which is the safest or greenest solvents for all applications,  
380 therefore the consideration of solvent remains a compromise between extraction yield,  
381 harmfulness and sustainable resource.<sup>41</sup>  
382 CHEM 21 toolkit demonstrated ethanol as the lowest PMI for curcuminoid extraction under ultra-  
383 sonication, therefore overall results suggested DES-B5 as the greenest performance for

384 curcuminoid extraction on account of excellent properties, including, high yields, biodegradability,  
385 low toxicity, being inexpensive and readily available.

386

## 387 **CONCLUSION**

388 Six conventional (hexane, DMF, toluene, ethyl acetate, ethanol and THF) and eighteen  
389 alternative green solvents (2-MeTHF, TMO, Cyrene and DESs) were employed to extract  
390 curcuminoids from turmeric powder using UAE technique. This is the first report of using Cyrene  
391 and TMO for curcuminoid extraction. Greener and bio-based solvents, namely ethanol, ethyl  
392 acetate, Cyrene and DES-B5 provided high effective extraction yield amongst those tested. DES-  
393 B5 with 10% water content exhibited advance extraction performance. The simple isolation of  
394 curcuminoid from the Cyrene and DES-B5 extracts was achieved by addition of water. Thereby  
395 avoiding the energy intensive solvent evaporation steps traditionally associated with high boiling  
396 point bio-based solvents. COSMO-RS modelling indicated that the extraction efficiency was not  
397 influenced directly by the polarity profiles of the solvents. The solubility test suggested that high  
398 solubility did not correlate with the efficiency of extraction. SEM images of plant matrix after  
399 extraction in DES-B5 indicated significant rupturing of cell walls, which corresponded to high  
400 extraction yields. Estimation of the green impact of conventional and green solvents for  
401 curcuminoid extraction, was achieved through the application of the CHEM21 guidelines. The best  
402 four solvents for curcuminoid extraction exhibited greater safety, low health issues and were more  
403 environmental-benign compared to dichloromethane. A PMI total of this proposed method of  
404 curcuminoid extraction with application of ultra-sonication offered 3 to 10 times better than  
405 previous literature methodologies. Therefore, it significantly improved a lower input mass per  
406 gram for curcuminoid extraction. Significantly, DES-B5 with 10% water content was

407 recommended as the greenest performance with several advantages, including high yields, low  
408 toxicity, bio-based solvent, being inexpensive, biodegradable and readily available for  
409 curcuminoid extraction. This work provides the basis for solvent selection in common natural  
410 product extraction and isolation by application of sustainable solvents and green metrics  
411 assessment. The bio-based solvent, 2-MeTHF was also used in curcuminoid extraction for the first  
412 time. Even though 2-MeTHF is a bio-based solvent with advantages against Cyrene, the extraction  
413 yield from 2-MeTHF was only moderate compared to Cyrene. However, it has potential to be used  
414 as a sustainable and alternative solvent for natural product extraction which should be further  
415 investigated.

416

#### 417 **Supporting information**

418 The identification and quantification of curcuminoids by HPLC; the calibration curves of  
419 curcuminoids; the extraction yields, dried crude extract and total curcuminoids in each solvent;  
420 impact of water content on Cyrene and extraction yields; investigation of solubility of curcumin;  
421 investigation and description of COSMO-RS modelling; SEM images; <sup>1</sup>H NMR spectra of  
422 curcuminoid standards.

423

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432

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## 550 **List of Figures and tables**

551 **Table 1** The choline chloride-based DESs.

552 **Table 2** List of conventional and green solvents and their properties.

553 **Table 3** Dried crude extract of curcuminoids and solubility of curcumin from green and  
554 conventional solvents.

555 **Table 4** Classification of selected solvents in this work according to CHEM 21 solvent selection  
556 guideline.

557 **Table 5** Process Mass Intensity (PMI) of each solvent for curcuminoid extraction from this work  
558 and previous work.

559 **Figure 1** Structures of Curcumin (**1**), Bisdemethoxycurcumin (**2**) and Demethoxycurcumin (**3**).

560 **Figure 2** The extraction yields of curcuminoids (mg/g) from conventional and alternative green  
561 solvents, under ultrasound-assisted extraction (UAE) at room temperature for 2 hours, and  
562 evaluated by RP-HPLC compared to standard.

563 **Figure 3** Extraction yields of curcuminoids (mg/g) from choline chloride-based deep eutectic  
564 solvents, by using ultrasound-assisted extraction (UAE) at room temperature for 2 hours, and  
565 evaluated by RP-HPLC.

566 **Figure 4 (a)** (a) The extraction yields of curcuminoids (mg/g) from DES-B5 varying solid-liquid  
567 ratio (1:6 to 1:21 ratio), by using ultrasound-assisted extraction (UAE) at room temperature for 2  
568 hours, and evaluated by RP-HPLC. (b) The extraction yields of curcuminoids (mg/g) from DES-  
569 B5 varying water content (0-40% v/v), by using ultrasound-assisted extraction (UAE) at room  
570 temperature for 2 hours, and evaluated by RP-HPLC.

571 **Figure 5** Selectivity of each solvent for three curcuminoids: curcumin, bisdemethoxycurcumin  
572 and demethoxycurcumin.

573 **Figure 6** SEM images of plant residues before (A, 500X) and after extraction with Cyrene  
574 (B, 500X) and DES-B5 (C, D: 500X).

575 **Figure 7** A proposed hydrogen-bond interaction between DES-B5 and plant cell walls (cellulose,  
576 hemicellulose and lignin).

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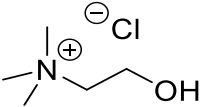
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586 **Table 1** The choline chloride-based DESs.

Solvents	Component		Molar ratio
	HBA	HBD	
DES-E1	Choline chloride	Ethylene glycol	1:2
DES-E2		Ethylene glycol	1:3
DES-E3		Ethylene glycol	1:4
DES-E4		Ethylene glycol	1:5
DES-E5		Ethylene glycol	1:6
DES-B1		1,4-Butanediol	1:2
DES-B2	1,4-Butanediol	1:3	
DES-B3	1,4-Butanediol	1:4	
DES-B4	1,4-Butanediol	1:5	
DES-B5	1,4-Butanediol	1:6	
DES-G1	Glycerol	1:2	
DES-G2	Glycerol	1:3	
DES-G3	Glycerol	1:4	
DES-G4	Glycerol	1:5	
DES-G5	Glycerol	1:6	

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592 **Table 2** List of conventional and green solvents and their properties.

Solvents	Kamlet-Taft parameters				Boiling point (°C)	Flash point (°C)	Density (g/mL)	M <sub>w</sub> (g/mol)
	$\alpha$	$\beta$	$\pi^*$	$E_T(30)$				
Hexane	0.00 <sup>20</sup>	0.00 <sup>20</sup>	-0.04 <sup>20</sup>	31.0	69 <sup>12</sup>	-26	0.661 <sup>12</sup>	86.2 <sup>12</sup>
Toluene	0.00 <sup>20</sup>	0.11 <sup>20</sup>	0.54 <sup>20</sup>	33.9	111 <sup>12</sup>	4	0.867 <sup>12</sup>	92.1 <sup>12</sup>
DMF	0.00 <sup>20</sup>	0.69 <sup>20</sup>	0.88 <sup>20</sup>	43.8	153	58	0.944	73.09
THF	0.00 <sup>20</sup>	0.55 <sup>20</sup>	0.58 <sup>20</sup>	37.4	66 <sup>12</sup>	-17	0.883 <sup>12</sup>	72.11 <sup>12</sup>
Ethyl acetate	0.00 <sup>20</sup>	0.45 <sup>20</sup>	0.55 <sup>20</sup>	38.1	77	-3	0.902	88.1
Ethanol	0.86 <sup>20</sup>	0.75 <sup>20</sup>	0.54 <sup>20</sup>	55.4	78	14	0.789	46.1
2-MeTHF	0.00 <sup>20</sup>	0.45 <sup>20</sup>	0.53 <sup>12</sup>	36.5	78 <sup>12</sup>	-10	0.854 <sup>12</sup>	86.1 <sup>12</sup>
TMO	0.00 <sup>12</sup>	0.77 <sup>12</sup>	0.35 <sup>12</sup>	-	112 <sup>12</sup>	4	0.802 <sup>12</sup>	128.25 <sup>12</sup>
Cyrene	0.00 <sup>11</sup>	0.61 <sup>11</sup>	0.93 <sup>11</sup>	-	203 <sup>11</sup>	108	1.25 <sup>11</sup>	128.13

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604 **Table 3** Dried crude extract of curcuminoids and solubility of curcumin from green and  
 605 conventional solvents.

Solvents	Dried crude extract (mg/g)	Total curcuminoids (mg/g)	Solubility of curcumin (mg/mL)
Hexane	25.63 ± 7.42	2.66	0.003 ± 0.00
Toluene	52.69 ± 1.64	8.22	1.75 ± 0.11
DMF	104.70 ± 12.40	32.30	>300
THF	84.73 ± 26.24	33.04	>300
Ethyl acetate	117.01 ± 9.18	54.17	26.49 ± 0.42
Ethanol	114.32 ± 3.87	56.03	7.19 ± 0.28
2-MeTHF	76.79 ± 20.17	31.77	71.79 ± 5.49
TMO	88.85 ± 8.73	21.74	2.27 ± 0.07
Cyrene	124.33 ± 5.13	52.85	83.23 ± 2.29
DES-B5 (10% H <sub>2</sub> O)	100.06 ± 1.57	55.86	6.55 ± 0.24

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615 **Table 4** Classification of selected solvents in this work according to CHEM 21 solvent selection  
 616 guideline.<sup>36</sup>

Solvents	Resource	BP (°C)	FP (°C)	Safety score	Health score	Env. score	Ranking by default	Ranking after discussion
Ethanol	Cereal crop <sup>37</sup>	78	14	4	3	3	recommended	recommended
Ethyl acetate	Cereal crop <sup>37</sup>	77	-3	5	3	3	recommended	recommended
Cyrene	Wood	203	108	1	2	7	problematic	problematic
TMO	Biomass <sup>12</sup>	112	4	1	5	5	problematic	problematic
Dichloromethane	Petroleum	40	n.a.	1	7	7	hazardous	hazardous

recommended	problematic	hazardous	Highly hazardous
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618 \*A solvent or chemical was not classified by CHEM 21 toolkit., n.a.: not available.

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629 **Table 5** Process Mass Intensity (PMI) of each solvent for curcuminoid extraction from this work  
 630 and previous work.

Solvents	Turmeric powder (g)	Weight of solvent (g)	Curcuminoids (g)	PMI total	PMI solvent
Ethyl acetate <sup>a</sup>	5	13.53	0.2709 <sup>b</sup>	68.4	50.0
Ethanol <sup>a</sup>	5	11.84	0.2802 <sup>b</sup>	60.1	42.2
Cyrene <sup>a</sup>	5	18.75	0.2643 <sup>b</sup>	89.5	71.0
DES-B5 (10% H <sub>2</sub> O) <sup>a</sup>	5	15.13	0.2793 <sup>b</sup>	71.9	54.1
TriA/Ethanol/H <sub>2</sub> O (36/24/40) <sup>16</sup>	4	16.00	0.0611 <sup>b</sup>	327.2	261.8
Ethanol <sup>16</sup>	4	16.00	0.0264 <sup>b</sup>	757.6	606.1
ChCl + Lac/Ethanol/TriA (35/27.5/37.5) <sup>40</sup>	2	16.00	0.0356 <sup>b</sup>	505.9	449.7
Dichloromethane <sup>21</sup>	600	3990	21.0438 <sup>c</sup>	218.1	189.6

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632 <sup>a</sup>This work. <sup>b</sup>A quantity of curcumin based on HPLC. <sup>c</sup>An amount of curcumin after isolation.

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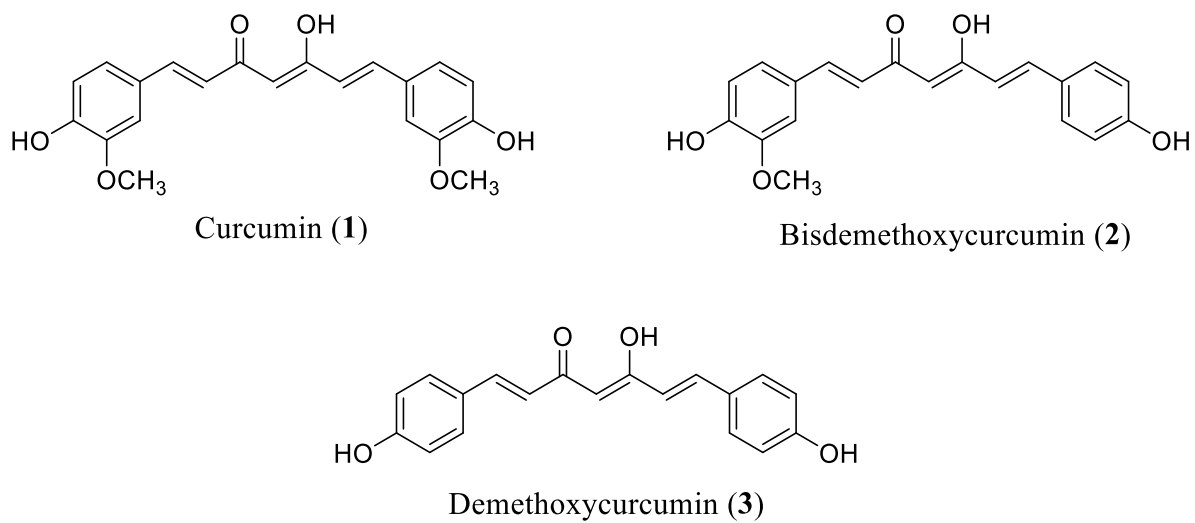
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642 **Figure 1** Structures of Curcumin (1), Bisdemethoxycurcumin (2) and Demethoxycurcumin (3).

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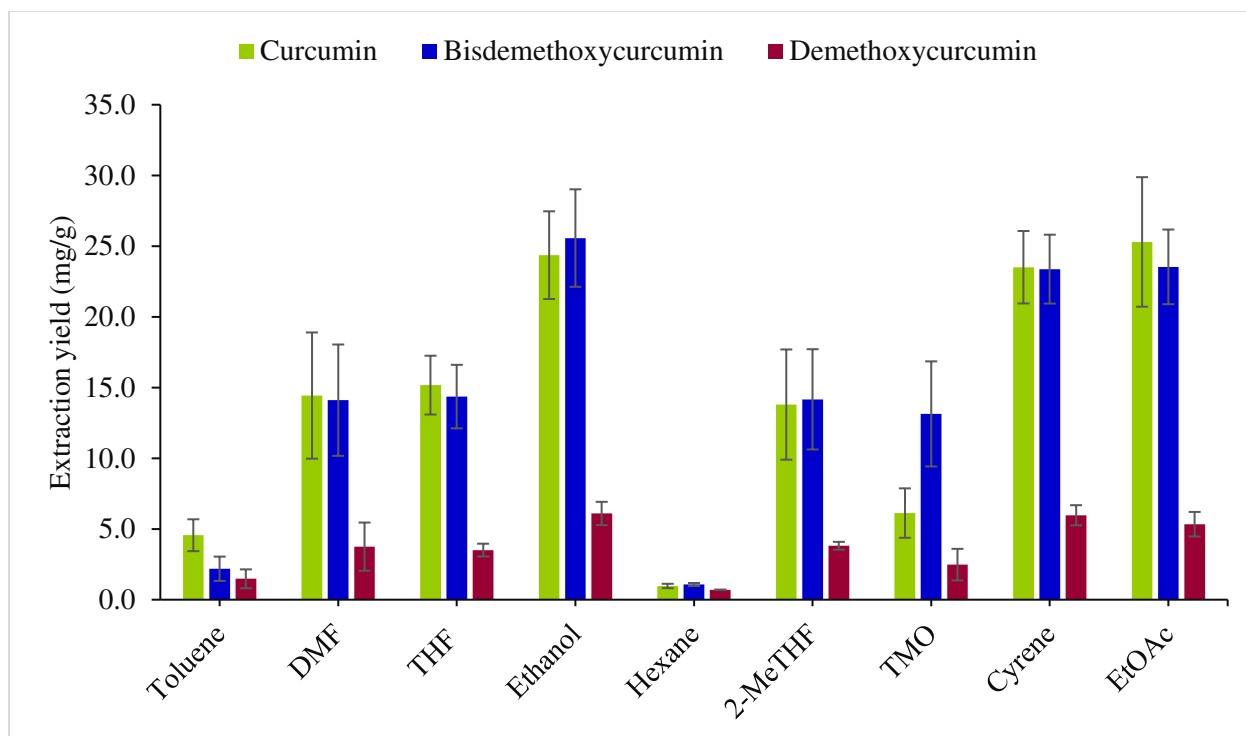
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651 **Figure 2** The extraction yields of curcuminoids (mg/g) from conventional and alternative green  
652 solvents, under ultrasound-assisted extraction (UAE) at room temperature for 2 hours, and  
653 evaluated by RP-HPLC compared to standard.

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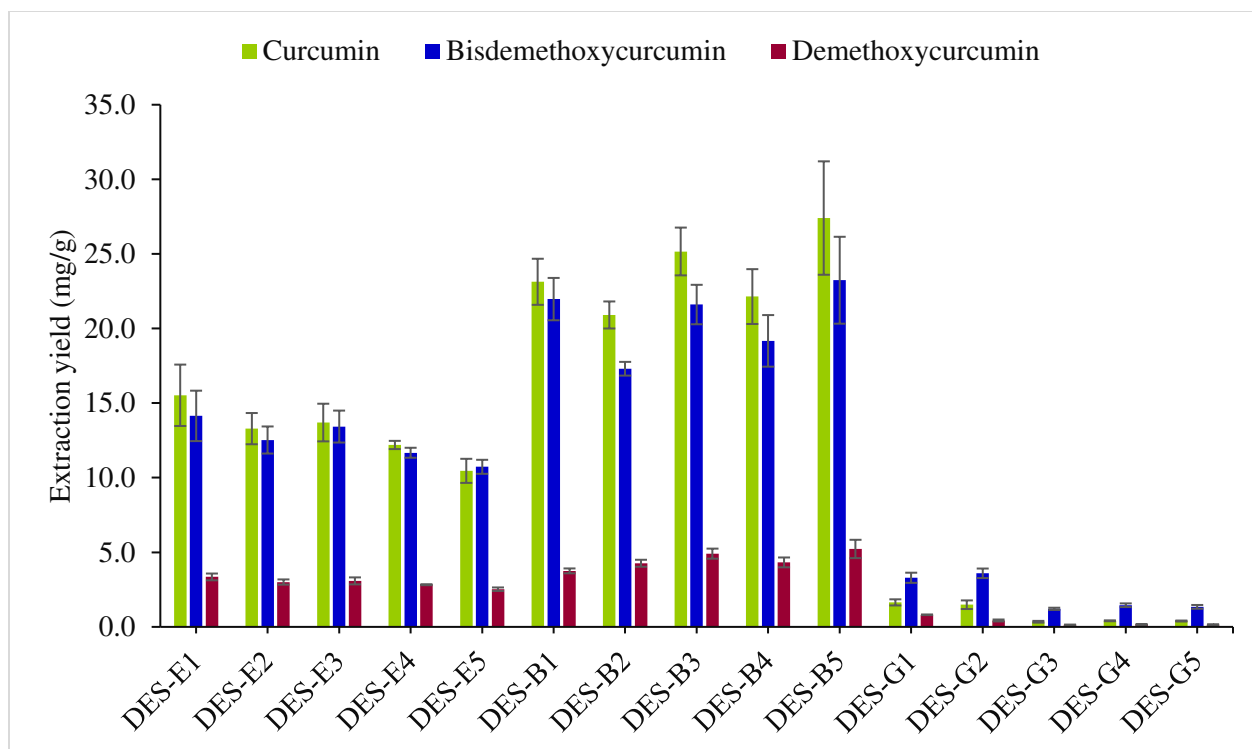
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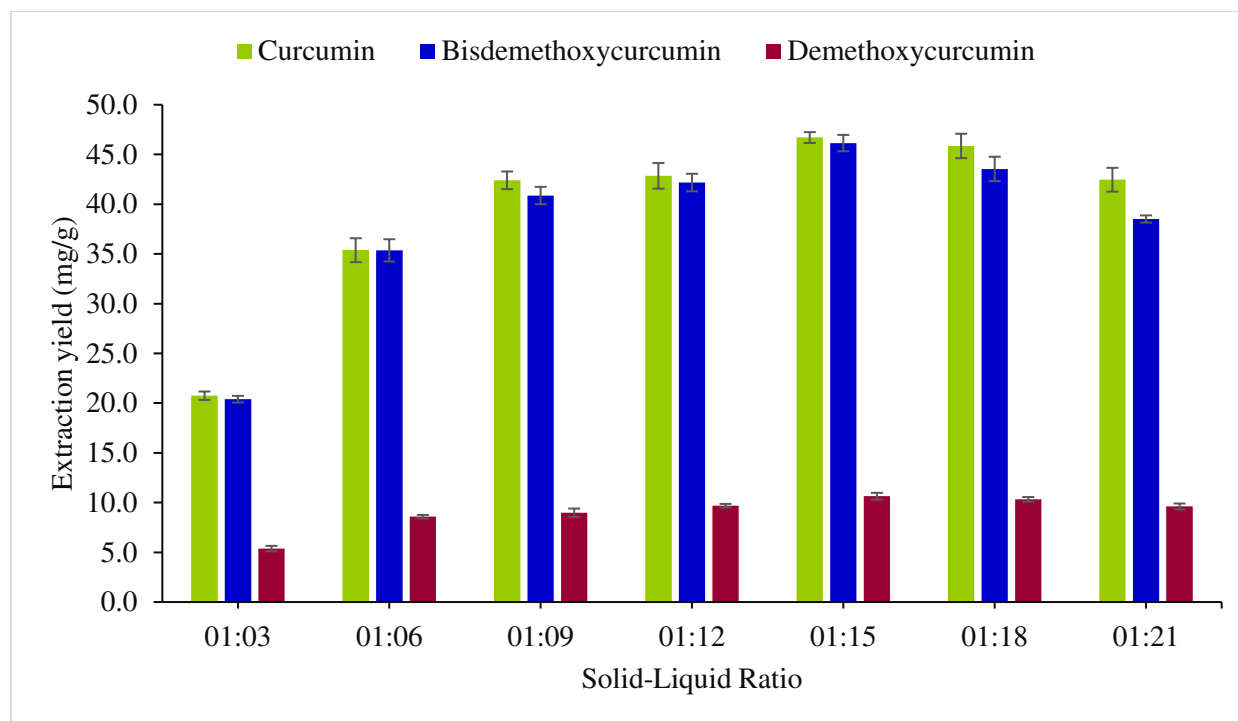
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663 **Figure 3** Extraction yields of curcuminoids (mg/g) from choline chloride-based deep eutectic  
664 solvents, by using ultrasound-assisted extraction (UAE) at room temperature for 2 hours, and  
665 evaluated by RP-HPLC.

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675 **Figure 4 (a)** The extraction yields of curcuminoids (mg/g) from DES-B5 varying solid-liquid ratio  
676 (1:6 to 1:21 ratio), by using ultrasound-assisted extraction (UAE) at room temperature for 2 hours,  
677 and evaluated by RP-HPLC.

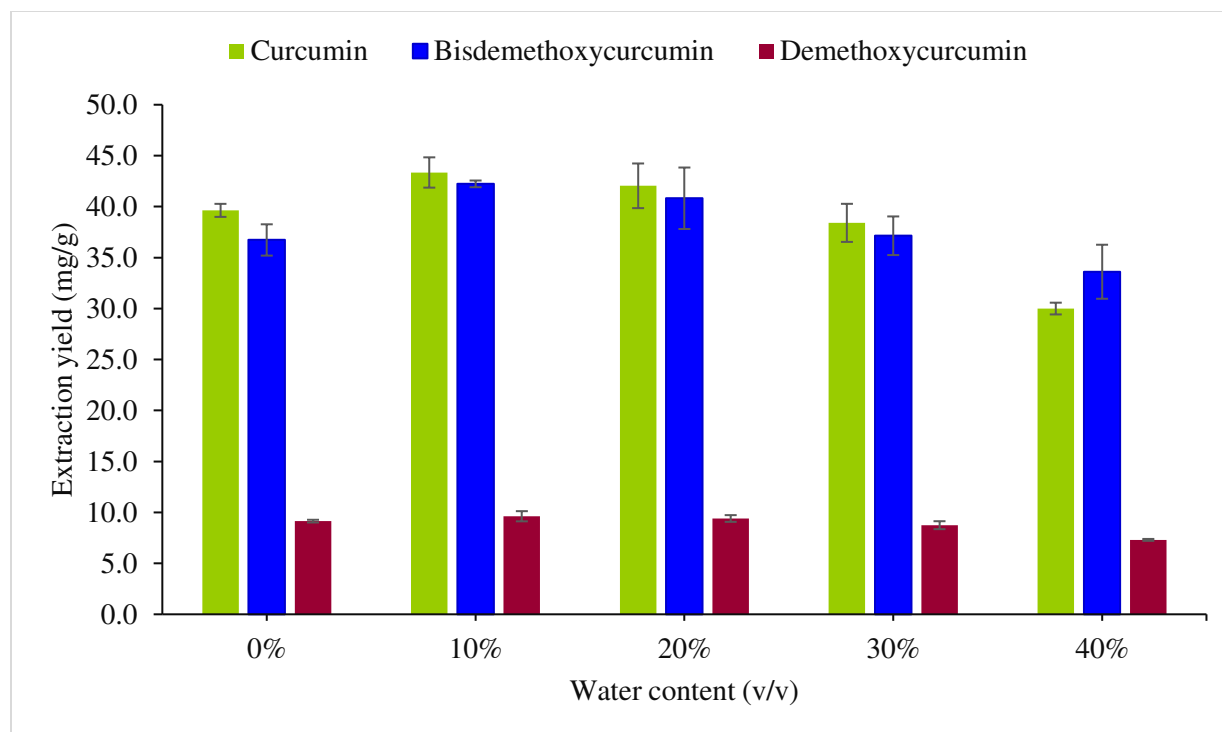
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685 **Figure 4 (b)** The extraction yields of curcuminoids (mg/g) from DES-B5 varying water content  
686 (0-40% v/v), by using ultrasound-assisted extraction (UAE) at room temperature for 2 hours, and  
687 evaluated by RP-HPLC.

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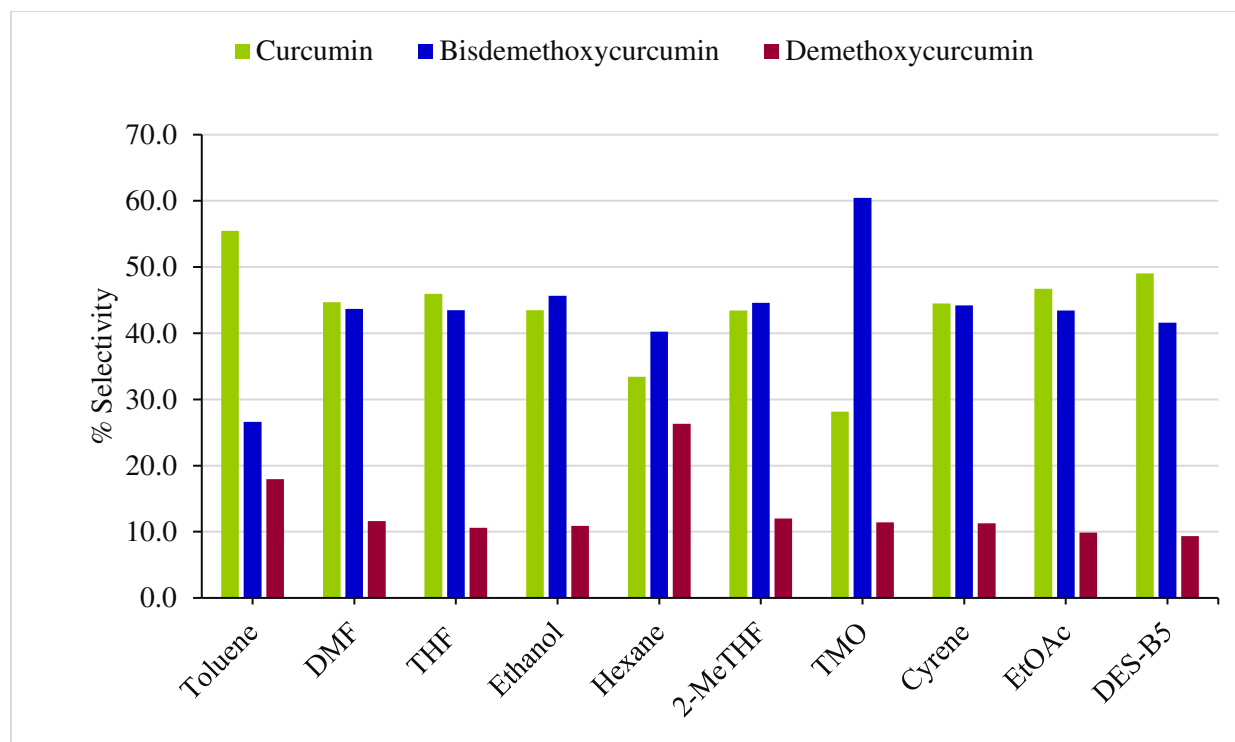
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699 **Figure 5** Selectivity of each solvent for three curcuminoids: curcumin, bisdemethoxycurcumin

700 and demethoxycurcumin.

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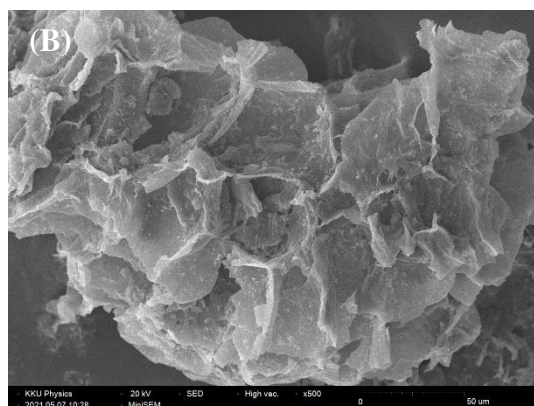
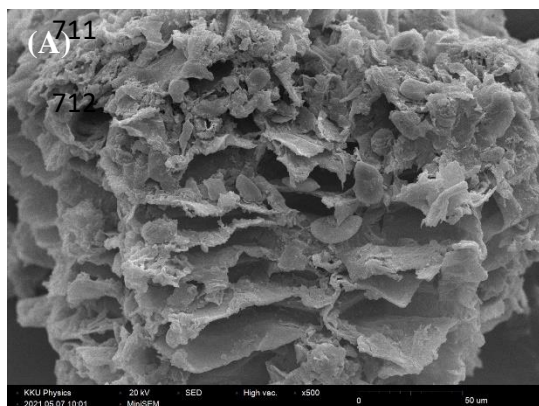
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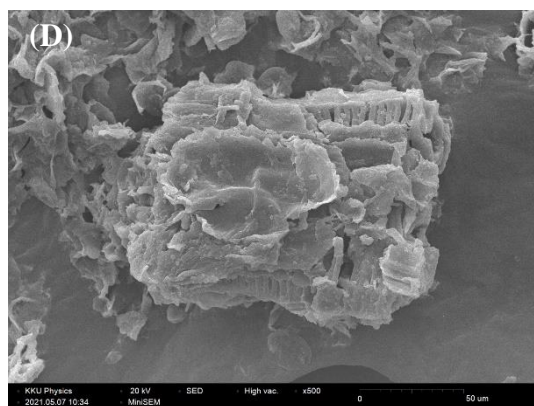
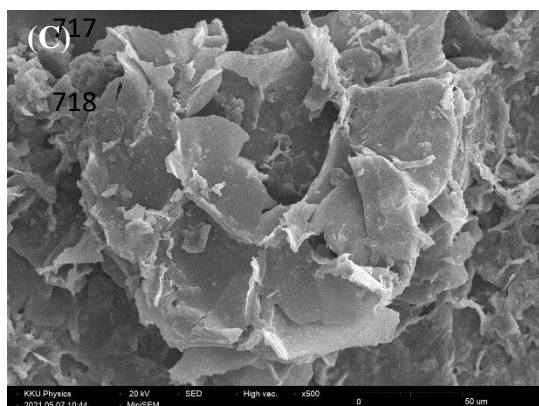


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724 **Figure 6** SEM images of plant residues before (A, 500X) and after extraction with Cyrene

725 (B, 500X) and DES-B5 (C, D: 500X).

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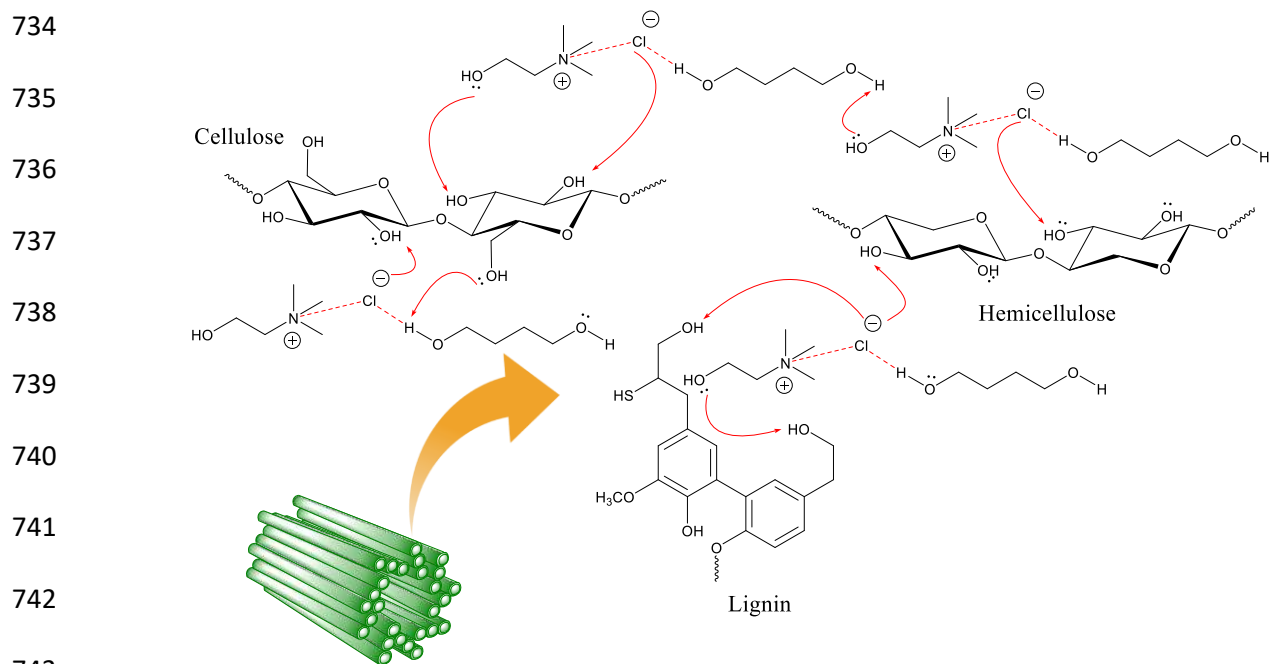
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745 **Figure 7** A proposed hydrogen-bond interaction between DES-B5 and plant cell walls (cellulose,  
746 hemicellulose and lignin).



759 **For Table of Contents Use Only**

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767 Sustainable and effective extraction of curcuminoids from *Curcuma longa* with several alternative

768 green solvents using ultrasound-assisted extraction