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

Rattikon Kisanthia[a], Andrew J. Hunt[b], James Sherwood[c], La-or Somsakeesit[d] and Chanokbhorn Phaosiri*[a]

[a] Natural Products Research Unit, Center of Excellence for Innovation in Chemistry, Department of Chemistry, Faculty of Science, Khon Kaen University, Khon Kaen, 40002, Thailand.

[b] Materials Chemistry Research Center (MCRC), Centre of Excellence for Innovation in Chemistry, Department of Chemistry, Faculty of Science, Khon Kaen University, Khon Kaen, 40002, Thailand.

[c] Green Chemistry Centre of Excellence, Department of Chemistry, University of York, Heslington, YO10 5DD, UK.

[d] Department of Chemistry, Faculty of Engineering, Rajamangala University of Technology Isan, Khon Kaen Campus, Khon Kaen, 40000, Thailand.

*Corresponding to: Dr. Chanokbhorn Phaosiri, Khon Kaen University

Email: chapa@kku.ac.th; Phone: 66-897119936; Fax: 66-4320-2373

ABSTRACT:

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

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

INTRODUCTION

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

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

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

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

EXPERIMENTAL SECTION

Materials

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

Plant material

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

Preparation of DES

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

Extraction of curcuminoids from *Curcuma longa*

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

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

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

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

HPLC Analysis

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

Isolation of curcuminoids from DES

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

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

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

ArgusLab (version 4.0.1, Mark Thompson and Planaria Software LLC, 2004, Seattle, WA, USA) was used to obtain approximate atomic coordinates of compounds. The conformations of the curcuminoids were calculated with COSMOconfX (version 4.0; COSMOlogic GmbH & Co. KG, Leverkusen, Germany, 2015). COSMOthermX (version C30_1705; COSMOlogic GmbH & Co. KG, 2017, TZVP basis set level) was used to provide molecular surface charges and execute the virtual experiments.

RESULTS AND DISCUSSION

Extraction of Curcuminoids from *Curcuma longa*

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

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

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

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

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

Optimization of the Curcuminoid Extraction Conditions

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

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

Recovery of curcuminoids from Cyrene and DESs Extracts

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

Comparison of curcuminoid selectivity

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

Exploration of Dissolving Mechanism Using COSMO-RS and Solubility Test

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

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

Destruction and Dissolution of the Plant Matrix in UAE

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

315 consistent with the literature.[35] 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.[36] 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.[38] 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.[38] 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

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

Evaluation and Comparison of Solvent Extraction Power Using CHEM21

The CHEM 21 green metrics toolkit was also used to assess an efficiency of curcuminoid extraction processes and was compared with two previous published sustainable methodologies.[16,40] The green metric selected for the assessment of the extractions was process mass intensity (PMI) (Table 5), the low PMI value referred to an effective method for extraction process. Ethanol extract in this work offered the lowest PMI total with 60.1 g/g, while ethyl acetate and Cyrene exhibited higher PMI with 68.4 g/g and 89.5 g/g, respectively. Although ethyl acetate offered the higher curcuminoid yield than ethanol, the PMI of ethyl acetate was greater than that of ethanol because of solvent density. Degot *et al.* extracted curcuminoids from turmeric powder using a mixture of triacetin (TriA)/Ethanol/H_2O (36/24/40% w/w) and pure ethanol under stirring at room temperature for 1 h, and the quantification of curcuminoids was evaluated by HPLC analysis.[16] Very recently, Huber *et al.* also extracted curcuminoids from turmeric rhizomes with NADES-based surfactant-free microemulsions (NADES-SFME, ChCl + Lactic acid/Ethanol/TriA

35/27.5/37.5% w/w) under the similar condition with Degot *et al*.[40] PMI calculations of two previously published extraction methods[16,40] with pure ethanol, a mixture of TriA/Ethanol/H_2O (36/24/40% w/w) and ChCl + Lactic acid/Ethanol/TriA (35/27.5/37.5% w/w), expressed higher total PMI with 757.6 g/g, 327.2 g/g and 505.9 g/g, respectively. Therefore, the methods utilising ethanol, ethyl acetate and Cyrene in this work demonstrate a significant improvement over previously published works. The PMI of the extraction process using DES-B5 was 71.9 g/g and demonstrated a higher value than that of ethanol and ethyl acetate, but lower than that of Cyrene. Moreover, the PMI of the traditional literature method employing dichloromethane for curcuminoid extraction was also estimated based on the quantity of curcuminoids recovered after column chromatography.[21] The PMI total of dichloromethane was calculated in this work using only the amount of starting material, solvent for extraction and the obtained curcuminoids from the previous work.[21] PMI total of dichloromethane as 218.1 g/g showed higher number than that of sustainable solvents in this work, namely ethanol, ethyl acetate, Cyrene and DES-B5. Even though the materials used for column chromatography not accounted for, this indirect comparison guided us that the low PMI of sustainable solvents (ethanol, ethyl acetate, Cyrene and DES-B5) offered the potential for substitution the highly hazardous solvent, dichloromethane. These results demonstrate that the proposed method of curcuminoid extraction with application of ultra-sonication significantly improved a lower input mass per gram for curcuminoid extraction. However, there is no universal solvent which is the safest or greenest solvents for all applications, therefore the consideration of solvent remains a compromise between extraction yield, harmfulness and sustainable resource.[41]

CHEM 21 toolkit demonstrated ethanol as the lowest PMI for curcuminoid extraction under ultra-sonication, therefore overall results suggested DES-B5 as the greenest performance for

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

CONCLUSION

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

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

Supporting information

The identification and quantification of curcuminoids by HPLC; the calibration curves of curcuminoids; the extraction yields, dried crude extract and total curcuminoids in each solvent; impact of water content on Cyrene and extraction yields; investigation of solubility of curcumin; investigation and description of COSMO-RS modelling; SEM images; ^{1}H NMR spectra of curcuminoid standards.

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List of Figures and tables

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

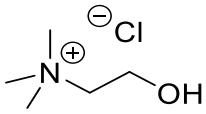
Figure 4 (**a**) (**a**) The extraction yields of curcuminoids (mg/g) from DES-B5 varying solid-liquid ratio (1:6 to 1:21 ratio), by using ultrasound-assisted extraction (UAE) at room temperature for 2 hours, and evaluated by RP-HPLC. (**b**) The extraction yields of curcuminoids (mg/g) from DES-B5 varying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

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

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

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

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			$E_T(30)$	Boiling point (°C)	Flash point (°C)	Density (g/mL)	M_W (g/mol)
	α	β	π^*					
Hexane	0.00[20]	0.00[20]	-0.04[20]	31.0	69[12]	-26	0.661[12]	86.2[12]
Toluene	0.00[20]	0.11[20]	0.54[20]	33.9	111[12]	4	0.867[12]	92.1[12]
DMF	0.00[20]	0.69[20]	0.88[20]	43.8	153	58	0.944	73.09
THF	0.00[20]	0.55[20]	0.58[20]	37.4	66[12]	-17	0.883[12]	72.11[12]
Ethyl acetate	0.00[20]	0.45[20]	0.55[20]	38.1	77	-3	0.902	88.1
Ethanol	0.86[20]	0.75[20]	0.54[20]	55.4	78	14	0.789	46.1
2-MeTHF	0.00[20]	0.45[20]	0.53[12]	36.5	78[12]	-10	0.854[12]	86.1[12]
TMO	0.00[12]	0.77[12]	0.35[12]	-	112[12]	4	0.802[12]	128.25[12]
Cyrene	0.00[11]	0.61[11]	0.93[11]	-	203[11]	108	1.25[11]	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_2O)	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.[36]

Solvents	Resource	BP (°C)	FP (°C)	Safety score	Health score	Env. score	Ranking by default	Ranking after discussion
Ethanol	Cereal crop[37]	78	14	4	3	3	recommended	recommended
Ethyl acetate	Cereal crop[37]	77	-3	5	3	3	recommended	recommended
Cyrene	Wood	203	108	1	2	7	problematic	problematic
TMO	Biomass[12]	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[a]	5	13.53	0.2709[b]	68.4	50.0
Ethanol[a]	5	11.84	0.2802[b]	60.1	42.2
Cyrene[a]	5	18.75	0.2643[b]	89.5	71.0
DES-B5 (10% H_2O)[a]	5	15.13	0.2793[b]	71.9	54.1
TriA/Ethanol/H_2O (36/24/40)[16]	4	16.00	0.0611[b]	327.2	261.8
Ethanol[16]	4	16.00	0.0264[b]	757.6	606.1
ChCl + Lac/Ethanol/TriA (35/27.5/37.5)[40]	2	16.00	0.0356[b]	505.9	449.7
Dichloromethane[21]	600	3990	21.0438[c]	218.1	189.6

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632 [a]This work. [b]A quantity of curcumin based on HPLC. [c]An amount of curcumin after isolation.

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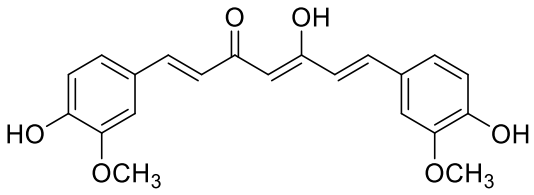
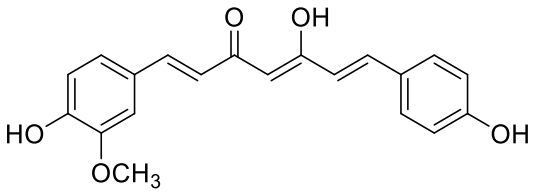
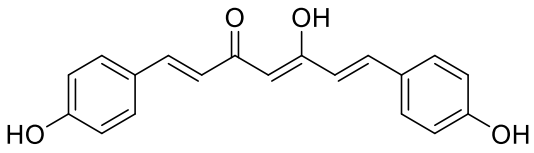


Curcumin (**1**)



Bisdemethoxycurcumin (**2**)



Demethoxycurcumin (**3**)

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

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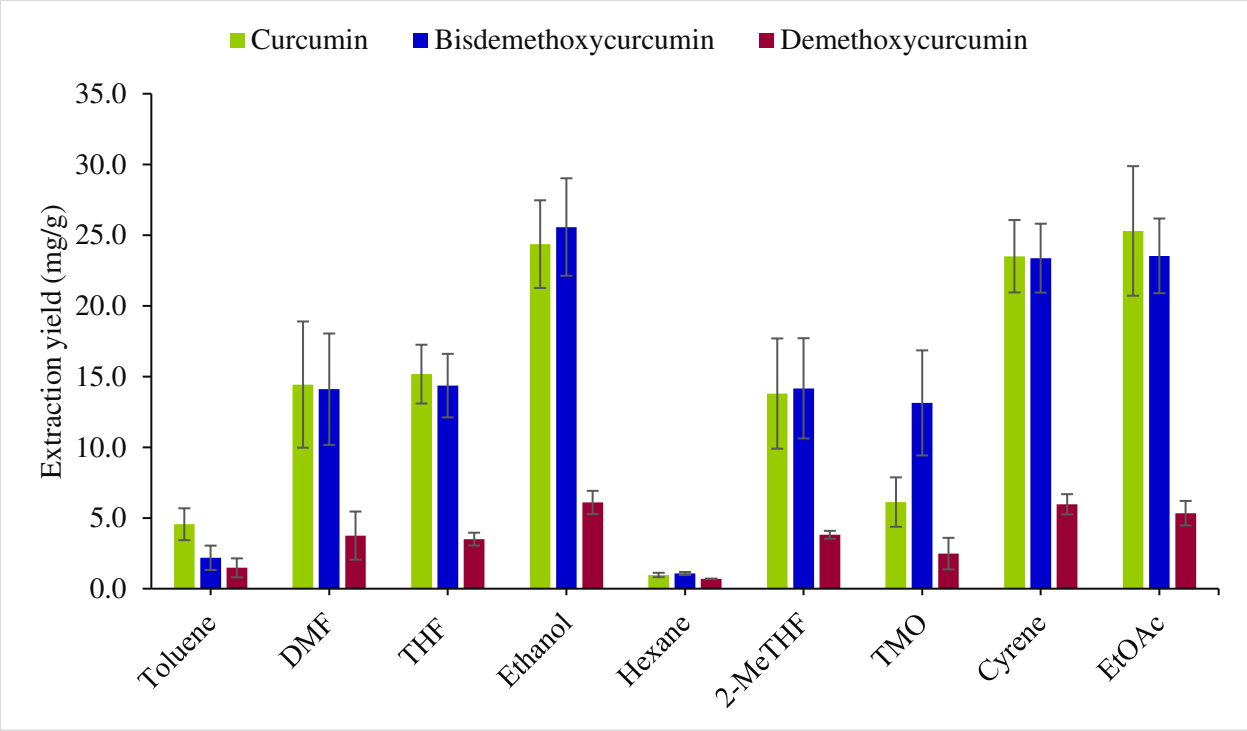
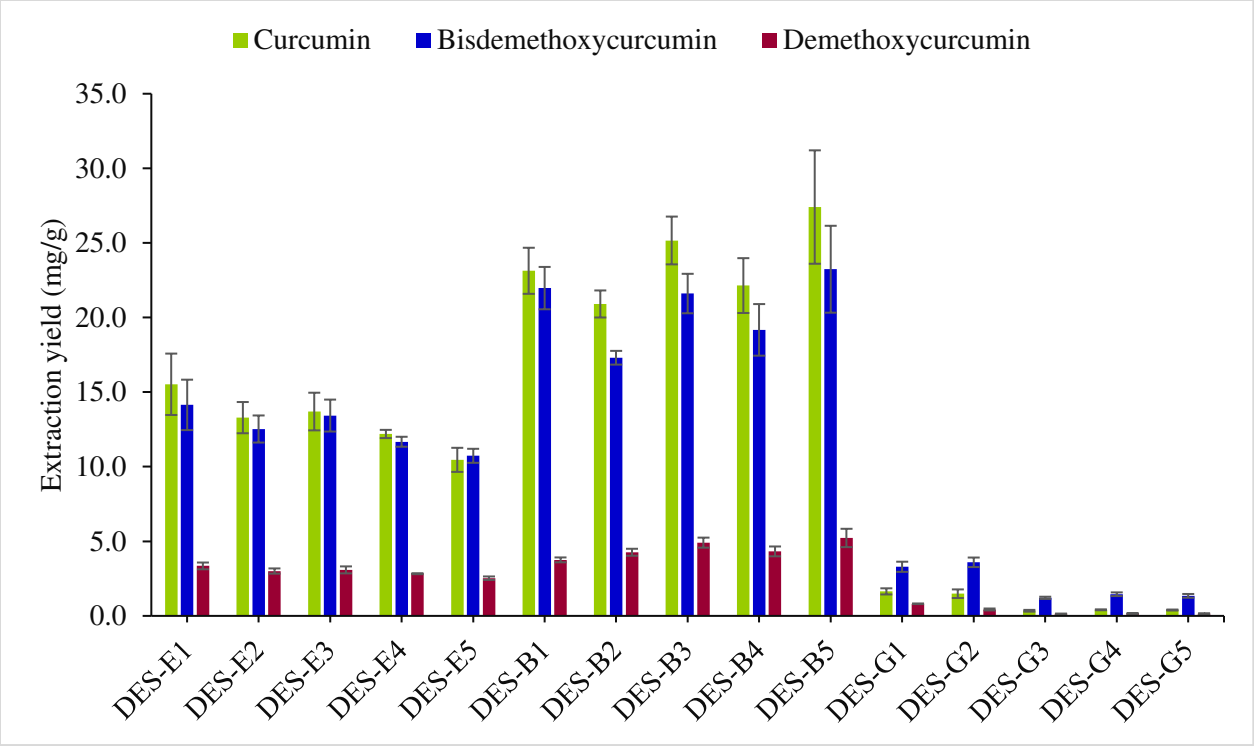


Figure 2 The extraction yields of curcuminoids (mg/g) from conventional and alternative green solvents, under ultrasound-assisted extraction (UAE) at room temperature for 2 hours, and evaluated by RP-HPLC compared to standard.



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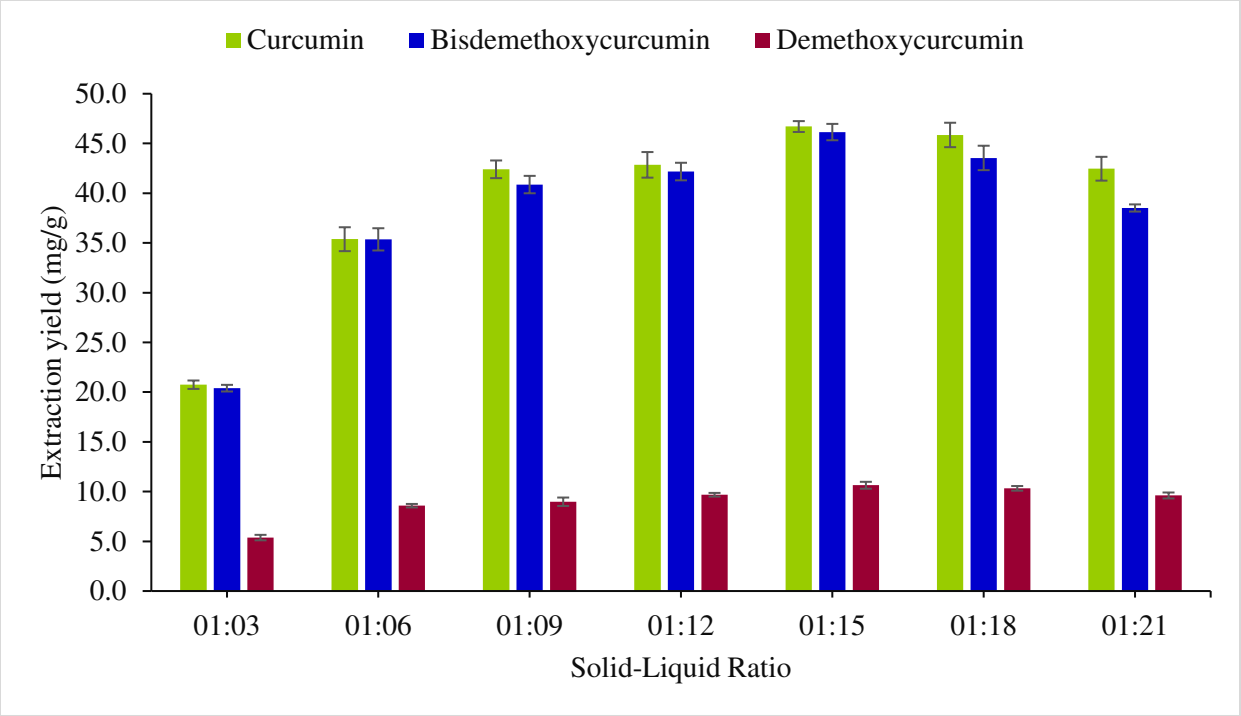

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675 **Figure 4** (**a**) The extraction yields of curcuminoids (mg/g) from DES-B5 varying solid-liquid ratio

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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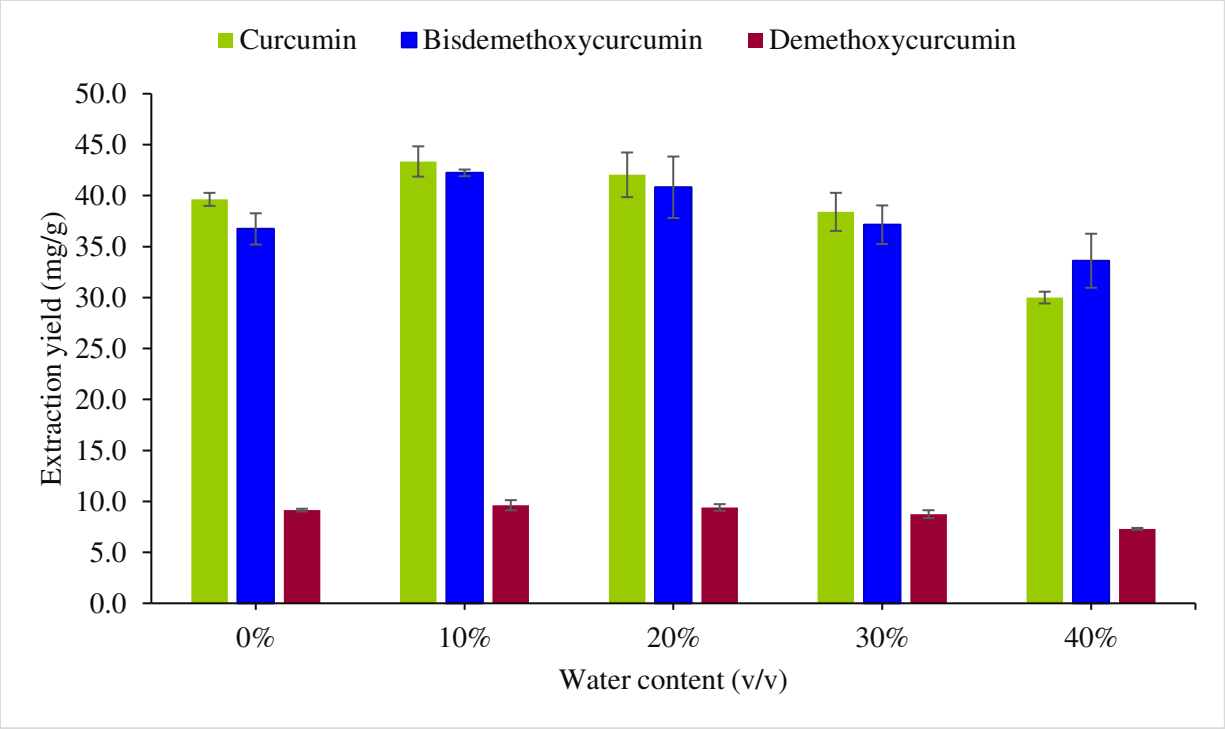
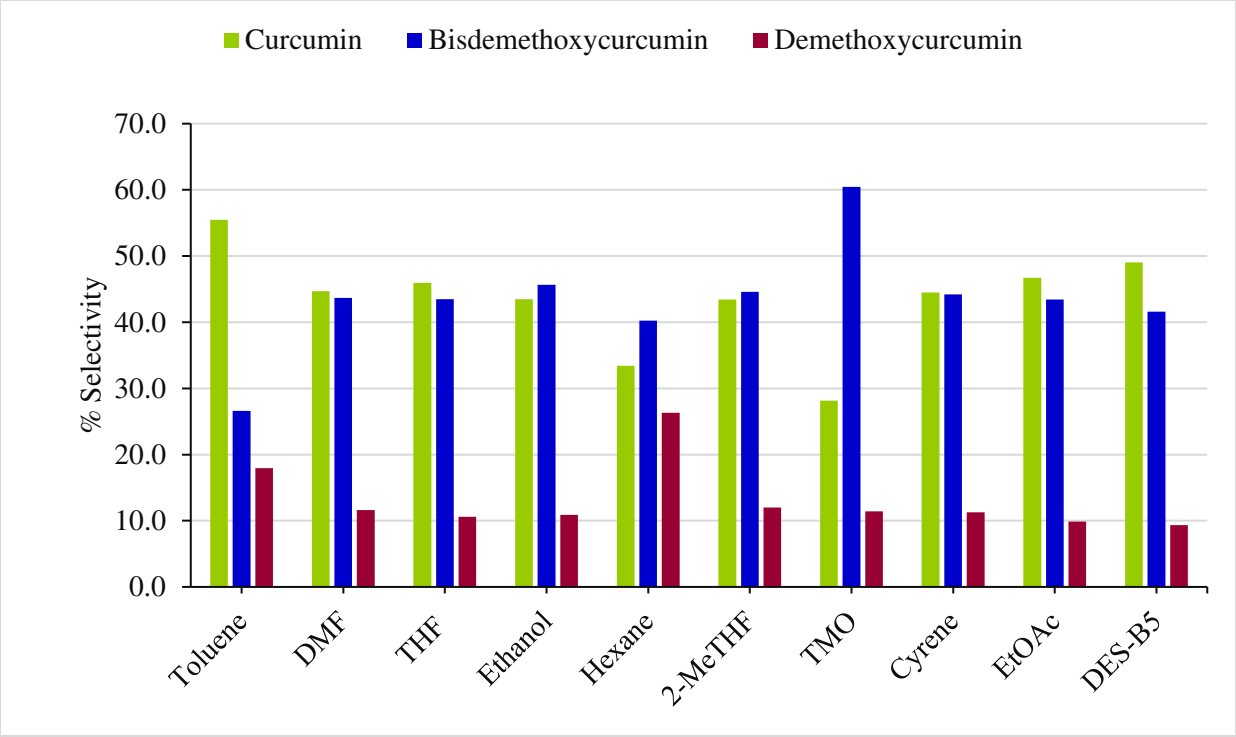


Figure 4 (**b**) The extraction yields of curcuminoids (mg/g) from DES-B5 varying water content (0-40% v/v), by using ultrasound-assisted extraction (UAE) at room temperature for 2 hours, and evaluated by RP-HPLC.



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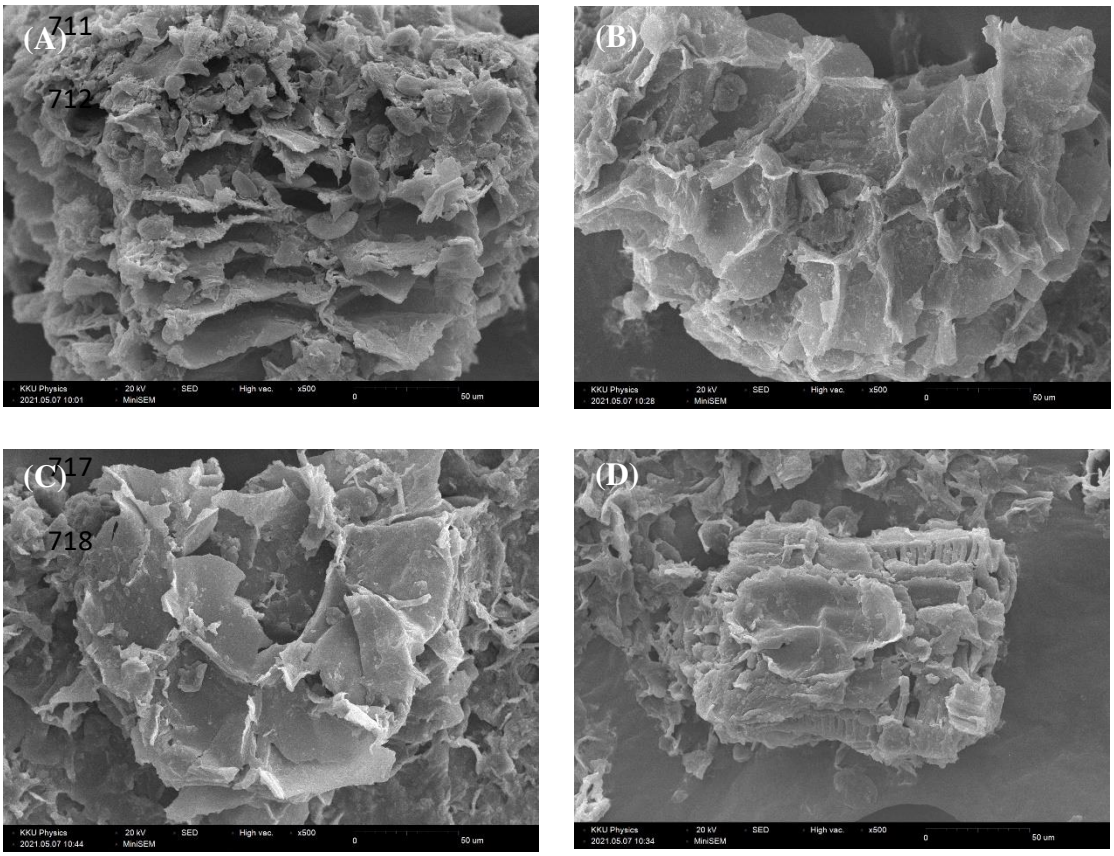

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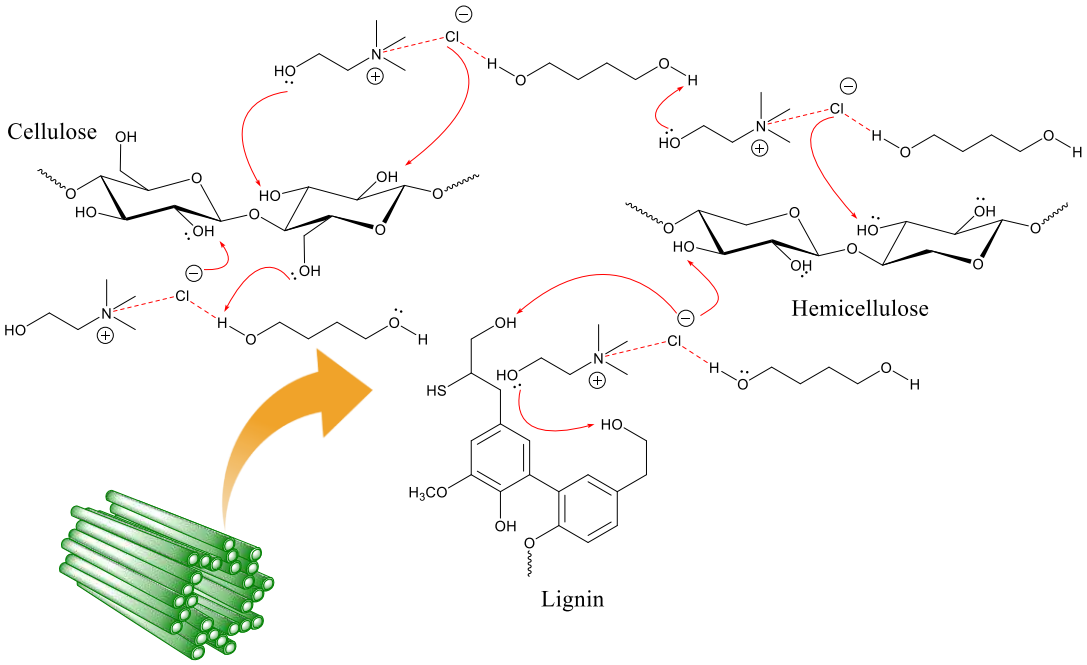

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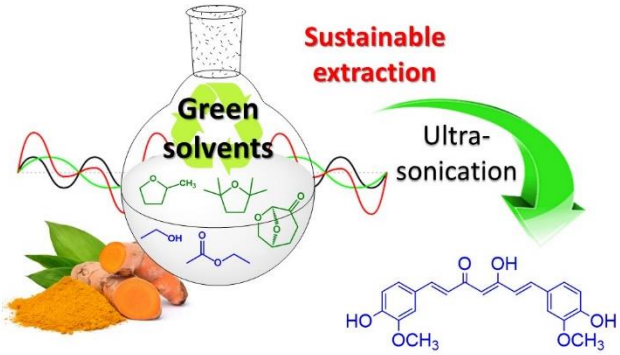

Sustainable and effective extraction of curcuminoids from *Curcuma longa* with several alternative green solvents using ultrasound-assisted extraction