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Repurposing orange peel waste for limonene extraction using *deep* eutectic solvents for cosmetic applications

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ABSTRACT

Orange peel waste, a byproduct of the citrus industry, can be valorized to obtain valuable compounds such as limonene, a terpene widely used in the food and cosmetics industry for its characteristic citrus aroma. Conventional extraction methods rely on organic solvents, which pose significant environmental concerns. To address this, *deep* eutectic solvents (*D*ES) have emerged as a sustainable alternative. In this work, we screened various *D*ES combinations using the COnductor-like Screening MOdel for Realistic Solvents (COSMO-RS), and the most promising systems containing compounds that are Generally Recognized as Safe (GRAS) or accepted by the Cosmetic Ingredient Review (CIR) were subsequently investigated experimentally. Polyethylene glycol 200 and 600 in combination with amino acids, sugars, carboxylic acids and urea were used for *D*ES formulation. Among them, PEG200-urea showed a significantly higher extraction yield of limonene *per* g of orange peel (2.7 mg g^{-1}) which is approximately 1.4x higher than that obtained with the reference organic solvent, heptane (1.9 mg g^{-1}). The limonene extracted with *D*ES remained stable for at least five weeks when stored at room temperature and in the dark. In addition, hesperidin, a high-value flavonoid for cosmetic applications, was successfully quantified in the extracts, while bergapten (a phototoxic furanocoumarin) and several limonene oxidation products were not detected. Our results show that *D*ES can achieve limonene yields comparable to, or higher than those of conventional extraction systems while presenting more sustainable metrics. This study emphasizes the potential of *D*ES for the sustainable limonene extraction from dried orange peels and contributes to circular economy initiatives.

1. Introduction

The food-processing industry generates substantial quantities of organic by-products annually, with a significant portion discarded as waste. This practice poses environmental challenges and contradicts sustainability principles. In response, the European Union has prioritized waste valorization as a key strategy to mitigate waste accumulation and promote a circular bioeconomy in line with its zero-

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waste objectives (European Commission. Directorate-General for Research and Innovation, 2018). Among these by-products, orange peels stand out as a particularly promising candidate for valorization, as oranges are among the most consumed fruits worldwide. According to FAOSTAT, nearly 70 million tons of oranges were harvested worldwide in 2023 (FAO, 2025), with orange peels accounting for up to 60 % of the total fresh weight (Ortiz-Sanchez et al., 2023). Additionally, up to 40 % of orange production is processed into orange juice, resulting in a large and stable supply of orange peels at industrial scale. Despite their abundance, disposing of orange peels poses a major challenge. Their low pH and high moisture content make them unsuitable for landfill, while excessive use in animal feed can cause digestive problems in livestock (Martín et al., 2010). Traditional disposal methods include incineration and composting, although the latter may be problematic due to the high limonene content in orange peels, which inhibits microbial activity at high concentrations (Siddiqui et al., 2022). In addition, limonene and its oxidation products can have phytotoxic and antimicrobial effects in composting environments, potentially delaying decomposition and affecting compost quality (Fagodia et al., 2017; Ruiz and Flotats, 2016). Orange peels are rich in valuable compounds, including essential oils, polyphenols, and pectin, which can be used to produce high-value products and address waste management issues (Gomez-Urios et al., 2025; Ortiz-Sanchez et al., 2024; Revathi et al., 2025; Senit et al., 2019). Recent efforts to valorize orange peels have focused producing activated carbon, bioethanol, and biogas (Ortiz-Sanchez et al., 2023; Siddiqui et al., 2022), but extracting valuable compounds, such as orange essential oil and other bioactive compounds (Senit et al., 2019), could broaden the range of products obtained and facilitate subsequent microbial treatment of the biomass by removing limonene.

Limonene is the predominant terpene in orange essential oil, comprising approximately 90–95 % of its composition. This colorless liquid has a sweet citrus scent and is widely used in various sectors, including the food industry, household cleaning products, agricultural pest control, and the coatings industry (Ciriminna et al., 2014; Pagliaro et al., 2023). Limonene is also present in many cosmetic products, such as skincare, bath, and hair care items, as well as makeup, perfumes, and deodorants, where it is typically used within general essential-oil safety limits (around 1 % for most products, up to 2 % for body products, 5 % for rinse-off or bath products, and no more than 0.25 % for baby products) (Geraldine Garrs, 2025).

In addition to its citrus scent, limonene provides several benefits, including anti-inflammatory, antioxidant, and antimicrobial properties (Han et al., 2021). Its widespread use is further supported by its classification as Generally Recognized as Safe (GRAS) by the U.S. Food and Drug Administration (FDA; 21 CFR Part 182).

Limonene is commonly extracted using traditional methods (*e.g.* mechanical cold pressing, water-based distillation, steam explosion and solid-liquid extraction (SLE)), which often rely on toxic organic solvents and high energy consumption, raising environmental concerns. These processes also require long extraction times and high investment costs (Siddiqui et al., 2022), and present challenges for extracting thermolabile compounds when high temperatures are necessary (Bitwell et al., 2023). In contrast, emerging greener extraction techniques, such as supercritical fluid extraction, microwave or ultrasound-assisted extraction and enzyme-assisted extraction, aim to enhance yield while minimizing environmental impact. However, these methods can also be energy-intensive and/or may still pose challenges, for instance the oxidation of limonene when water is used as the extraction medium (since it accelerates autoxidation to peroxides, epoxides and oxygenated terpenes, especially under exposure to air and light (Li et al., 2018)), or the continued reliance on organic solvents, which are environmentally problematic (de la Torre et al., 2019; Gavahian et al., 2019; Siddiqui et al., 2022).

In recent years, *deep* eutectic solvents (*D*ES) have emerged as promising alternatives for the extraction of bioactive compounds from natural sources (Gomez-Urios et al., 2025; Socas-Rodríguez et al., 2021; Zannou et al., 2025) due to their greener character, biocompatibility, and cheaper and easier preparation (Smith et al., 2014). The versatility of *D*ES allows the formation of numerous combinations (Martins et al., 2019), however, the experimental evaluation of all these combinations is both costly and time-consuming, highlighting the need for computational screening methods (Ozturk et al., 2019). The COnductor-like Screening MOdel for Realistic Solvents (COSMO-RS) offers a reliable and robust solution, utilizing quantum chemistry and statistical thermodynamics to predict the thermodynamic properties of fluids and solutions (Klamt, 2018).

One of the main challenges in using *D*ES for extraction is the difficulty of isolating target compounds from these solvents, which often requires additional purification steps. To address this limitation, *D*ES composed of GRAS ingredients and/or ingredients accepted by the Cosmetic Ingredient Review (CIR) were selected, enabling their direct incorporation into cosmetics. This strategic approach aligns with green chemistry principles, leverages the multifunctional role of *D*ES in both extraction and formulation, and advances beyond the current state-of-the-art of primarily using choline chloride-based *D*ES for limonene extraction. Therefore, this study aims to extract limonene from orange peels using sustainable solvents, mild temperatures, and ambient pressure conditions, employing methodologies that can be easily implemented at industrial scale. Here, we compare computational predictions made by COSMO-RS with experimental results to confirm that the selected solvents are suitable for cosmetic applications, thus eliminating the need for further purification processes and leveraging the solvents' synergistic properties. Furthermore, the extracts have been examined for additional beneficial compounds, while also investigating the presence of other monoterpenes, including potential oxidative byproducts of limonene, to ensure both effective extraction of limonene and its stability in the final product.

2. Material and methods

2.1. Materials

R(+)-Limonene (98 %, Fluka), linalool (97 %, Acros organics), (R)-(−)-carvone (98 %, Merk), (+)-limonene oxide (97 %, *cis/trans* mixture, Merk), L-carveol (95 %, *cis/trans* mixture, Sigma-Aldrich), bergapten (99 %, Sigma-Aldrich), hesperidin (≥80 %, Sigma-Aldrich), (±)-naringenin (≥95 %, Sigma-Aldrich), quercetin (≥95 %, Sigma-Aldrich), and (−)-epicatechin (≥90 %, Sigma-Aldrich) were used as standards. Heptane (≥99.0 %, Emsure), methanol (≥99.8 %, J. T. Baker), ethanol (≥99.9 %, Carlo Erba), acetone (≥99.5 %, Honeywell) and ethyl acetate (≥99.5 %, Honeywell) were used as conventional organic solvents for extractions. For the preparation of *D*ES, polyethylene glycol 200 (PEG200) and 600 (PEG600), polypropylene glycol 400 (PPG400), D-sorbitol (Sor; ≥98.0 %), L-proline (Pro; 99 %), L-lysine (Lys; ≥98.0 %), gallic acid (Gall.A; 97.5–102.5 %) levulinic acid (Lev.A; ≥97 %), DL-tartaric acid (≥99 %), citric acid (≥99.5 %), L-ascorbic acid (≥99 %), D(−)-xylose (≥99 %), glycine (99.1–101 %), xylitol (≥99 %), myristic acid (99 %), myristil alcohol (97 %), were purchased from Sigma-Aldrich. Additional components included urea (≥99.5 %; Thermo Fischer), L-(+)-arginine (>99 %; TCI America), stearic acid (≥98 %; Carl Roth), palmitic acid (98 %; Acros Organics), D-glucose (Glu; ≥99.5 %, Merck), and D (−)-fructose (≥99 %; Merck).

2.2. COSMO-RS computational evaluation

The solubility of limonene was first explored *in silico* using COSMO-RS. The model was used to predict the activity coefficients at infinite dilution (γ^{∞}) of limonene in pure compounds or their mixtures. This property reflects the behavior of solute molecules surrounded by solvent molecules, making it a good initial measure of the theoretical separation performance of the solvent. To this end, the geometry of each molecule was previously optimized using the TmoleX software package (Steffen et al., 2010) (interface of TURBOMOLE) and the COSMO-BPTZVP template, which includes a def-TZVP basis set, density functional theory (DFT) with the B–P83 functional level of theory, and the COSMO solvation model (Steffen et al., 2010). The default TURBOMOLE convergence criterion was applied, *i.e.*, the self-consistent field (SCF) energy convergence threshold was set to 1×10^{-6} Hartree. A single conformer was optimized for each molecule, and the structural information for limonene was obtained from the COSMOtherm TZVP database. PEG400 and PPG400 structural information was obtained through molecular dynamics simulations according with the procedure described elsewhere (Silva et al., 2023). Next, the γ^{∞} of limonene in pure solvents and their mixtures at 50 °C were computed via the COSMOtherm® software (Version 21.0) package with the BP_TZVP_21.ctd parametrization (Eckert and Klamt, n.d.) using the most stable conformers. The mixtures were treated as binary mixtures at a fixed stoichiometric ratio (Resende et al., 2024). A database of commonly used solvents in industry and in the extraction of bioactive compounds was compiled based on literature and is available in Table S1 of Supporting Information (SI).

2.3. Biomass preparation and characterization

The oranges Lane Late (*Citrus sinensis*) were purchased from the local supermarket in February 2024. They were first washed thoroughly with water and dried with a paper towel. They were cut in half and squeezed with a citrus juicer, mimicking the process from the beverages industry. Orange peels were then cut into smaller pieces and placed in an oven at 35 °C for 48 h to dry. After drying, the biomass was blended into a powder, and its particle size distribution was characterized by manual sieve analysis (ISO 3310), showing that most particles were predominantly smaller than 1.0 mm, with the largest fraction (36.3 ± 0.4 %) in the 0.5–0.150 mm size range. To assure comparable dryness of every batch, the water content was determined using the HE53 Moisture Analyzer (Mettler Toledo, USA) and was approximately 9 %. The powdered orange peels were stored in the dark at room temperature until use.

2.4. DES preparation

Based on the COSMO-RS results, we selected a few HBA and HBD for experimental testing. In selecting suitable HBAs and HBDs, the focus was mainly on compounds that are acceptable for the cosmetics industry and its applications (*i.e.* GRAS ingredients and/or ingredients accepted by the CIR). Several combinations of HBAs and HBDs were tested by mixing them in specified molar ratios, namely 1:1, 1:2 and 2:1. Ratios of 1:1 and 1:2 consistently resulted in either solid or highly viscous systems that exhibited poor homogeneity at room temperature, making them unsuitable for extraction experiments. In contrast, the 2:1 ratio produced liquids with adequate fluidity and stability at room temperature for all *D*ES combinations studied; therefore, this ratio was consistently used throughout the extraction experiments. Moreover, since water content plays an important role in *D*ES formulation, water was added in varying amounts (0–20 wt%) at the beginning of *D*ES preparation. Therefore, its content in the liquid chemicals was measured using Karl Fischer titration, while the solid chemicals were analyzed using the HE53 Moisture Analyzer to correct the water concentration in the *D*ES for the water already present in the chemicals. The initial water content in each compound is summarized in Table S2 of SI. The *D*ES was formulated by mixing HBD, HBA and water with magnetic stirrers at 80 °C for 2 h until clear, homogeneous liquids were obtained. After the *D*ES was prepared, it was cooled to room temperature and stored at room temperature until use. Density and viscosity measurements of the prepared mixtures were carried out at atmospheric pressure and at 25 °C and 50 °C using an automated Anton Paar SVM 3000 rotational Stabinger viscometer-densimeter. The temperature uncertainty was ±0.02 K, the relative uncertainty in dynamic viscosity was ±0.35 %, and the absolute uncertainty in density was $\pm 5 \times 10^{-4}$ g cm^{-3}.

2.5. Solid-liquid extraction (SLE) of limonene

SLE of orange peels was performed in 100 mL reactors on a Carousel 6 Plus Reaction System (Radleys, UK). The orange peels were combined with each solvent in a 1:10 solid-to-liquid ratio and mixed with a magnetic stirrer at 250 rpm for 120 min at 50 °C. Details of method development can be found in SI. The extractions were performed using the selected *D*ES and a few organic solvents for comparison with conventionally used solvents. After the extraction, the samples were centrifuged to separate the biomass from the supernatant under the following conditions: (i) room temperature, 10 min and 4500 rpm when using organic solvents, and (ii) two-centrifugation rounds at 10 min, 10 000 rpm, and 40 °C when using *D*ES due to their higher viscosity. The extractions were performed in triplicates, with average and standard deviation determined and presented.

The determination of limonene in the extracts was performed by gas chromatography-mass spectrometry (GC-MS). However, extracts containing *D*ES cannot be injected directly into the GC–MS system due to the low vapor pressure of *D*ES components. Therefore, an additional liquid–liquid extraction (LLE) step was required to transfer the analyte into a GC–MS-compatible solvent. Through previous experiments and method optimization (*i.e.* solvent selection, mixing technique, temperature, time, and number of cycles; cf. SI for more details), the optimal conditions were identified to achieve high extraction yields and good repeatability. The LLE was performed with heptane in 1:1 (vol%) ratio to the *D*ES extract. The mixture was vertically rotated (Bio RS-24 Mini-rotator, Biosan) at maximum speed for 40 min at 40 °C. Afterwards, the phases were left to separate, followed by additional centrifugation at 3500 rpm for 10 min at 30 °C. The phases were physically separated using a syringe and the top (heptane-rich) phase was submitted for GC-MS analysis.

To accurately calculate the limonene concentration, the efficiency of the LLE needed to be considered. As such, the LLE efficiency was assessed using limonene standard dissolved in pure *D*ES. Besides limonene concentration in the heptane-rich phase, the volume and weight of both phases were also monitored before and after the LLE to accurately examine the behavior of liquid-liquid system.

2.6. *Conventional extraction of limonene*

To comprehensively evaluate the effectiveness of *D*ES-based extractions, a comparison was made with Soxhlet extraction, a widely used standard technique. Since the selected *D*ES are not volatile, they could not be used in the Soxhlet extraction, therefore, only organic solvents were used for these extractions. Initially, the extraction temperature for each organic solvent was optimized to ensure an equal number of cycles for all solvents and mimic the total time as was used for SLE (cf. SI for more details). Due to the volumetric restrictions of the Soxhlet apparatus (volume 100 mL, Isolab; extraction thimble MN 645, Macherey-Nagel, Germany), a smaller solid-to-liquid ratio (1:40) between orange peels and solvent was used in comparison to SLE. These experiments were conducted during earlier method optimization stages, with extractions performed using fresh orange peels (Navelina, purchased from the local supermarket in July 2023) cut into approximately (0.5 × 0.5) cm pieces. Additional, SLE was carried out with the same sample preparation to facilitate a comparison between extraction techniques (cf. SI for more details). The extractions were conducted in duplicates at minimum, and the extracts were stored in the refrigerator at 4 °C until analysis with GC-MS.

2.7. *Characterization of the extracts*

Limonene, along with other volatile analytes such as linalool, and possible oxidation products like carvone, carveol, and limonene oxide, were examined using gas chromatography coupled to a single quadrupole mass detector with electron ionization and a flame ionization detector (GC-MS/FID system; QP2010 Ultra Shimadzu, Japan). The GC was equipped with a Zebron ZB5-MSi 60 m column (Phenomenex) and helium as a carrier gas, operating with a column flow rate of 1.78 mL min^{-1}. The injection volume and temperature were set to 0.5 μL and 270 °C, respectively, and the split ratio was 80. The separation gradient started with a 6 min hold at 80 °C, followed by an increase of 10 °C min^{-1} up to 140 °C, then by 20 °C min^{-1} to 290 °C, and a final hold at 290 °C for 8 min. Before analysis all the samples were filtered through 0.2 μm CHROMAFIL Xtra PTFE-20/13 filters. Identification of the analytes was carried out using MS detector in scan acquisition mode (35–500 Da) by comparing the chromatographic spectra with the NIST spectral library and retention times (RT) with standard compounds. However, since the analytes were successfully separated, quantitative analysis was performed using an FID detector, which exhibited lower instrument drift at longer time periods.

The extracts were also examined for non- or semi-volatile compounds by ultra high-performance liquid chromatography–diode array detection system (HPLC-DAD; Ultimate 3000RS, Thermo Scientific, U.S.A). The detection method was optimized for bergapten, as the representative of toxic furanocoumarins found in orange oil, as well as several beneficial flavonoids such as hesperidin, naringenin, quercetin, and epicatechin. The column used was Hypersyl GOLD (3 μm, 4.6 × 150 mm, Thermo Scientific) with mobile phases A (miliQ water) and B (methanol), both containing 0.1 vol% formic acid, selected based on previous experiences. The elution gradient consists of an isocratic hold at 20 % B for 1 min, followed by ramp to 95 % B over 1–18 min, hold at 95 % B for 3 min, and final equilibration to 20 % B for 9 min. The flow rate was 0.4 mL min^{-1} and the oven temperature was 30 °C. The injection volume was 10 μL, and each sample was previously diluted 100 times with 50 % aqueous methanol to reduce the viscosity of the *D*ES. The detection wavelengths were set at 310 nm for bergapten and 284 nm for hesperidin and other flavonoids. Analyte identification was achieved by comparing RT and UV-VIS spectra with the standard compounds.

In both analytical methods, the samples were quantified using standard calibration curves. The limit of detection (LOD) was calculated based on a 3-fold signal-to-noise ratio, and the limit of quantification (LOQ) was calculated as a 10-fold signal-to-noise ratio and are provided in the SI (Table S3). The final concentrations were expressed as mg of analyte *per* g of orange peel, accounting for LLE efficiency when using *D*ES solvents and GC-MS detection. The detailed calculation procedure is provided in the SI (Eqs. (1)–(4)).

2.8. *Statistical analysis*

The experimental results were compared using statistical analysis in the R program with the rstatix package. Initially, the normality of distributions was assessed using the Shapiro-Wilk test and Q-Q plot, while the homogeneity of variance was examined using Levene's test. Subsequently, the comparison of multiple samples as is the influence of non-PEG components and comparisons of *D*ES with reference organic solvent was made by using ANOVA and Tukey HSD post hoc test and the comparison of two samples, such as the impact of water or PEG molar mass, was done with *t*-test and Holm method for adjusting p-values.

The overall workflow adopted in this study is summarized in Fig. 1.

3. Results & discussion

3.1. Computational evaluation of solvent effectiveness using COSMO-RS

In previous studies, we successfully demonstrated the utility of the COSMO-RS thermodynamic tool for selecting *D*ES to extract biomolecules from several biomass sources by predicting activity coefficients at infinite dilution (Contieri et al., 2023; Resende et al., 2024; Wojeicchowski et al., 2020). In the current study, we first validated the potential of COSMO-RS by comparing the predicted $\ln \gamma^{\infty}$ with experimental data from the literature on limonene extraction from orange peels (Battista et al., 2020; Bica et al., 2011; Li et al., 2022; Ma et al., 2019; Ozturk et al., 2019; Panić et al., 2021). As shown in Fig. S1, solvents with lower $\ln \gamma^{\infty}$ values tend to extract more limonene, indicating a greater tendency to interact and solubilize the solute. This qualitative agreement validates the use of COSMO-RS for the desired extraction. A quantitative correlation was not expected, as the γ^{∞} describes solute – solvent affinity rather than extraction yields, which are additionally governed by many physical factors, such as mass-transfer and matrix effects. It is important to note that no direct correlation was established between calculated and experimental values, due to variations in orange species and extraction parameters in the literature data.

Before further studies, and to better understand limonene nature, the σ-profile and σ-potential of the molecule were calculated using the COSMO-RS model (Fig. S2). The σ-potential values of limonene are positive in both negative and positive screening charge densities, indicating that limonene has little tendency to interact with hydrogen-bond donor or acceptor groups. This indicates that limonene is non-polar, and that hydrophobic interactions are the dominant and most favorable interactions (Ozturk and Gonzalez-Miquel, 2019).

After validating COSMO-RS in the benchmarking study, 26 traditional solvents were evaluated for their effectiveness in extracting limonene from orange peels, and ranked based on their $\ln \gamma^{\infty}$ values as depicted in Fig. 2. Non-polar solvents such as dimethyl ether, diethyl ether, cyclohexane, and hexane were found to be potentially effective (low $\ln \gamma^{\infty}$ values) but pose significant environmental and health risks due to their flammability and toxicity (Dirgha Raj Joshi Nisha Adhikari, 2019). On the other hand, while highly polar solvents like water and glycerol are environmentally benign, they exhibited high $\ln \gamma^{\infty}$ values, indicating poor effectiveness in limonene extraction. This is expected, as limonene has very low polarity and, consequently, very limited solubility in water (Fichan et al., 1999) and in glycerol. Heptane stands out as a balanced choice, combining a moderate $\ln \gamma^{\infty}$ value with more favorable environmental characteristics compared to hexane, which is commonly used for extracting limonene (Siddiqui et al., 2022). Therefore, heptane will serve as a reference and traditional solvent in the experimental phase.

Subsequently, the investigation was expanded to include 167 additional solvents (listed in Table S1), selected based on the literature and representing molecules typically used in the formulation of *D*ES. The computed $\ln \gamma^{\infty}$ of these pure solvents and their equimolar mixtures are displayed in Fig. 3. *D*ES were sorted according to their chemical family and arranged using a color scale, where those with high dissolving power – lower $\ln \gamma^{\infty}$ – are colored in dark green, while the less effective ones – higher $\ln \gamma^{\infty}$ – are shown in darker orange. The diagonal line corresponds to pure components.

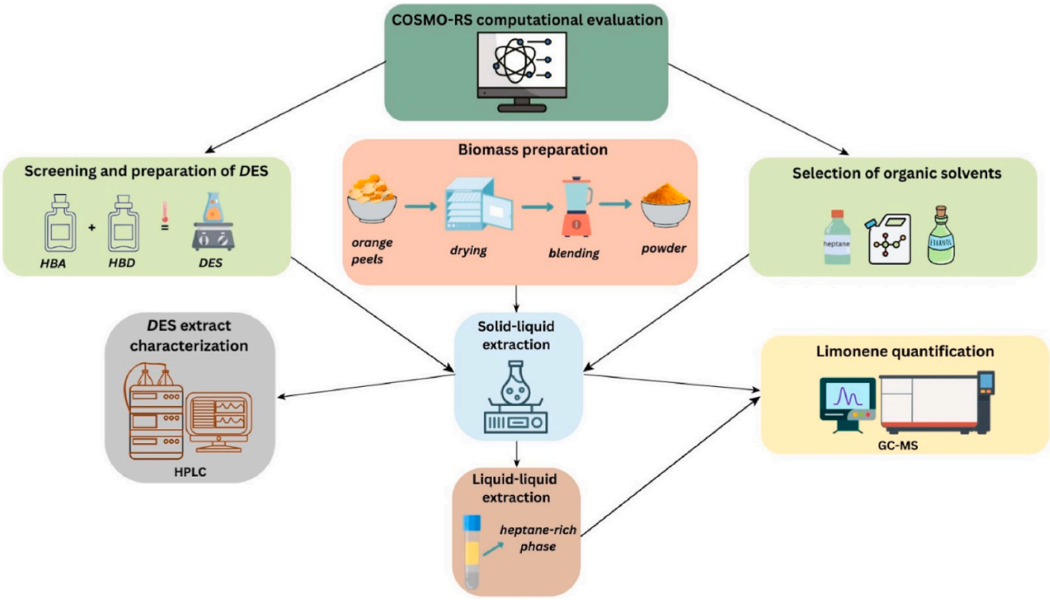

Fig. 1. Schematic overview of the experimental and computational workflow developed in this study.

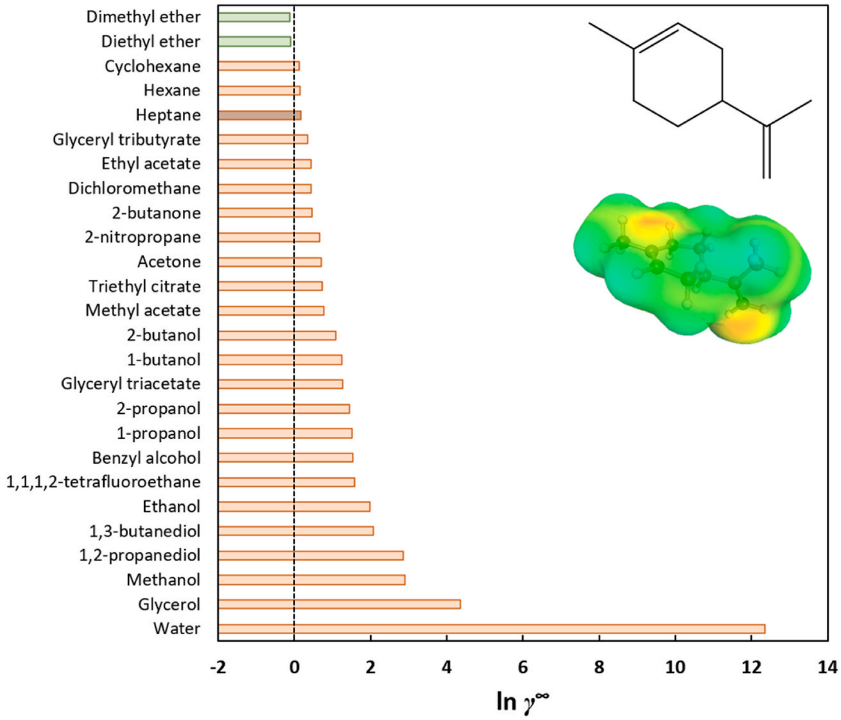

Fig. 2. Graphical representation of the logarithm of the γ^∞ of limonene in various traditional solvents at 50 °C, as predicted by the COSMO-RS model. Orange bars indicate ln $\gamma^\infty > 0$ (reduced affinity), while green bars indicate ln $\gamma^\infty < 0$ (favorable solubility). The dashed vertical line corresponds to ln $\gamma^\infty = 0$. The chemical structure of limonene and its COSMO surface representation is included as an inset.

Considering limonene's hydrophobic nature, it is anticipated that the most effective *D*ES would be those formulated from hydrophobic HBAs and HBDs, such as fatty acids or even other terpenes like thymol. Moreover, the addition of water is expected to negatively impact its solubility, as we previously observed in the extraction of carnosic acid and carnosol from rosemary (Wojeicchowski et al., 2020). In fact, from Fig. 3, it can be seen that mixtures formed between alcohols, fatty acids, phenols, ethers, esters and/or terpenes result in lower ln γ^∞ values for limonene, confirming that the solubility is dominated by the hydrophobicity of the *D*ES.

However, the intention of this study is to provide a limonene extract compatible with cosmetic applications, so the focus was placed on selecting GRAS compounds and/or compounds listed by the CIR that showed promising COSMO-RS results (*i.e.* lower ln γ^∞ values for limonene). The allowed concentrations for some components are listed in Table S4. Limonene itself has a very strong smell and is therefore only used at very low concentrations in cosmetic products, generally within established essential-oil safety guidelines (around 1 % for most products) (Geraldine Garrs, 2025). For this reason, terpenes are not suitable for our application. Furthermore, their strong smell would completely overpower the desirable limonene scent of oranges. The best results with low γ^∞ values with the majority of components were obtained with trioctylphosphine oxide (TOPO; the bottom row in Fig. 3), but unfortunately TOPO is not considered GRAS nor is it accepted by CIR, as it causes skin irritation, is toxic to aquatic organisms (ChemBK database), and recent research also indicates possible neuro-muscular toxicity (Niemuth et al., 2021). Therefore, it is not suitable for the desired application.

Despite not being typical hydrophobic *D*ES, interesting results emerged from mixtures involving PEG400 (ln γ^∞ in pure PEG 400 = 0.53) and HBDs of different polarities, suggesting a synergistic effect. Examples include mixtures of PEG400 with short-chain alcohols like 1-propanol (ln γ^∞ in pure 1-propanol = 1.53 and ln γ^∞ equimolar mixture = 0.82), carboxylic acids like benzoic acid (ln γ^∞ in pure benzoic acid = 1.87 and ln γ^∞ equimolar mixture = 0.98), and even the molten salt tetrabutylammonium bromide (ln γ^∞ in pure tetrabutylammonium bromide = 0.73 and ln γ^∞ equimolar mixture = 0.63), known for its high solubility in water (Vilas-Boas et al., 2020). However, benzoic acid and tetrabutylammonium bromide can cause skin irritation, so other appropriate HBDs were selected for experimental investigation with PEG as HBA. Based on this, the akin PEG200 and PEG600 HBAs with HBDs from different chemical families were selected for the subsequent experimental phase, including amino acids, sugars, carboxylic acids, and amides. Even though, some of those groups did not show exceptional results in COSMO-RS computations, they are frequently used in cosmetics and lead to beneficial properties of the final products (Burnett et al., 2013; Misra and Shrivastava, 2020; Yu and Van Scott, 2004) and are therefore worth investigating in combination with PEG. PPG, a more hydrophobic polymer, also showed promising results on COSMO-RS so it was submitted for experimental testing.

Since most *D*ES exhibit high viscosity due to extensive hydrogen bonding networks, which can hinder extraction and limit penetration through the peel's biological barriers, the effect of water addition was also experimentally evaluated. Moreover, the HBA:HBD ratio was adjusted to ensure that the mixtures remain liquid at room temperature.

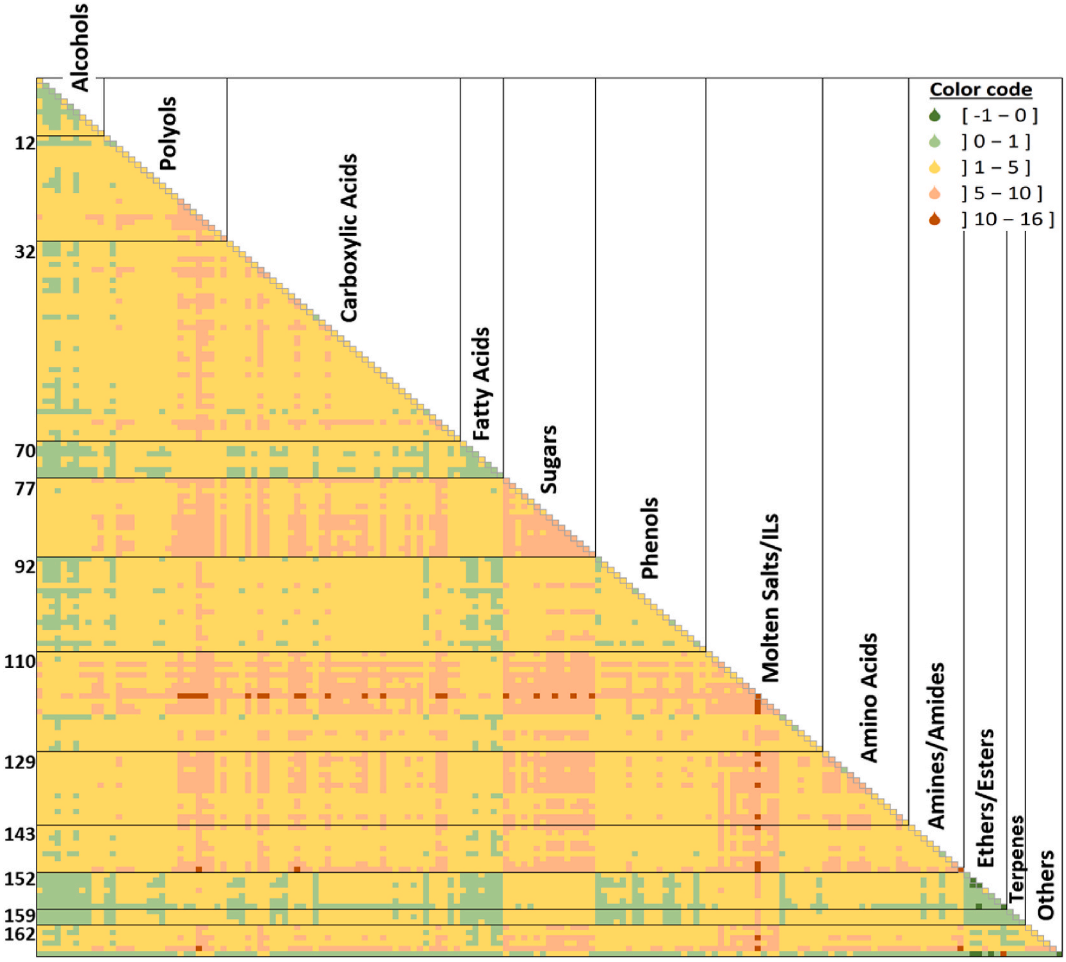

Fig. 3. Graphical representation of the logarithm of the γ^{∞} of limonene in eutectic solvents (1:1) at 50 °C, as predicted by the COSMO-RS model. Each colored cell corresponds to one eutectic solvent system, as listed in Table S1. Eutectic solvents are grouped by chemical family, as indicated along the axes.

3.2. Conventional extraction of limonene using organic solvents

Organic solvents were used as a representative of more traditional extraction methods so that they could later be compared with the alternative extraction using *D*ES. Based on COSMO-RS calculations, we found that the solubility of limonene is mainly influenced by hydrophobic interactions. Therefore, it can be assumed that more hydrophobic organic solvents will present better extraction efficiency. As shown in Fig. 3, all selected organic solvents were able to extract limonene from orange peels, albeit in varying concentrations, using the same method and biomass as in the *D*ES extractions. Among the organic solvents tested, heptane proved to be the solvent that extracted the highest limonene concentration (1.93 ± 0.04 mg limonene *per* g of dried orange peel), which is consistent with the prediction of COSMO-RS, as it is the most non-polar organic solvent. The experimental extraction also yielded interesting results in the case of ethyl acetate and methanol, which are not in agreement with the predictions of COSMO-RS. Ethyl acetate was predicted to be the second-best organic solvent, and the polar organic solvent methanol was predicted to be the least efficient among the organic solvents tested. However, experimental extractions showed the opposite effect: ethyl acetate was one of the least efficient organic solvents and methanol showed one of the highest extraction yields for all extraction and pretreatment conditions tested, including SLE with dry, powdered orange peels and Soxhlet and SLE with wet, cut-to-pieces orange peels (Fig. S3). These results show that the solubility of limonene, as predicted by COSMO-RS, is not the only factor affecting extraction yield. In fact, COSMO-RS does not capture solvent – matrix interactions, and polar solvents such as methanol can enhance biomass permeability and cell wall swelling, thereby improving limonene release despite their lower predicted solubility.

Similar results were presented by Xhaxhiu et al. (2013) where the non-polar solvent hexane extracted significantly less limonene from orange peels than methanol in the Soxhlet extraction. However, when the polarity was increased by testing a mixture of hexane: acetone in a 1:1 ratio, the extraction yield improved significantly and was even higher compared to methanol. These results suggest that polar organic solvents interact better with the biomass and provide better cell permeability, which could be the reason for the higher extraction yield with methanol than expected in our case. On the other hand, Ozturk et al. (2019) and Ma et al. (2019) reported similar extraction efficiencies of limonene from orange peels for hexane and ethyl acetate. The observed discrepancies could be due to different methods used or a different orange variety, which was also observed in our experiments. When comparing the SLE and Soxhlet methods, and accounting for the standard deviation, no significant differences in extraction efficiency were observed, except in the case of ethanol. Soxhlet extraction is commonly used as a benchmark for evaluating new extraction methods due to its high efficiency through solvent recycling. However, these findings challenge the assumption that Soxhlet extraction is always superior, particularly for volatile compounds. This highlights the crucial role of solvent selection in extraction processes and suggests that SLE can be an effective alternative in certain cases to achieve satisfactory yields.

3.3. *Experimental DES formation*

*D*ES offer a promising alternative to conventional organic solvents for extraction processes. COSMO-RS calculations showed that PPG and PEG gave promising results, which prompted us to investigate the formation of *D*ES using various combinations of PEG and PPG with alcohols, carboxylic acids, sugars, amino acids, polyols, and fatty acids. Initially, we prepared *D*ES combinations with HBD and HBA molar ratios of 1:1, 1:2, and 2:1, and without water. COSMO-RS analysis suggested that the solubility of limonene is primarily influenced by the hydrophobicity of the solvent, so compounds with long carbon chains such as fatty alcohols and fatty acids are among the best theoretically predicted HBDs. The combinations of PPG400 with fatty acids (stearic, palmitic, and myristic acids) and PEG200 with C-14 long-chain compounds (*i.e.* myristic acid and myristil alcohol) resulted in homogeneous mixtures, but this occurred only at elevated temperatures (above 45 °C for combinations with fatty acids and above 35 °C for combination with fatty alcohol). Therefore, these were not considered here since for the target application (cosmetics), *D*ES are required to be liquid and stable at room temperature. The formation of *D*ES with PPG400 and other compounds was also mostly unsuccessful, as homogeneous mixtures were not obtained with the selected carboxylic acids (tartaric, citric, ascorbic, and gallic acids), sugars (fructose, glucose, and xylose), amino acids (arginine, glycine, lysine, and proline), polyols (sorbitol and xylitol), and urea. In contrast, PEG200 and PEG600 successfully formed *D*ES with several HBDs, namely the amino acids lysine and proline, the polyols sorbitol and xylitol, the sugars glucose, fructose and xylose, the carboxylic acids gallic acid and levulinic acid, and urea. *D*ES containing urea, levulinic acid, and gallic acid formed without the addition of water, whereas others required a small addition of water to facilitate the formation of a stable liquid. A 20 wt% water addition was sufficient to obtain homogeneous liquids that remained stable at room temperature. Most of the *D*ES formed exhibited high viscosity, making them difficult to handle and limiting solvent penetration into the biomass (Vilková et al., 2020). In addition, handling viscous solvents on an industrial scale (*e.g.* mixing) is energy-intensive and costly. While water-free *D*ES are expected to be more hydrophobic and potentially better for limonene dissolution, *D*ES with low amount of added water also showed promise for experimental extractions. A lower viscosity and easier formation of *D*ES was also observed at 2:1 PEG:HBD molar ratio compared to 1:1 and 1:2, making it a more favorable choice for limonene extraction. The 13 *D*ES selected for the experimental limonene extraction are listed in Table 1.

With the aim of identifying the optimal *D*ES for limonene extraction, three different experiments were conducted to investigate the effects of (i) various HBDs, (ii) the addition of water to the *D*ES, and (iii) different molecular weights of PEG. It should be noted that, although in this work we classify PEG as HBA and the other compounds as HBD, this categorization is not always straightforward. Many of these compounds contain a mix of functional groups, such as hydroxyl groups, which can act as either HBD or HBA, as well as ether linkages or carbonyl groups, which can also act as HBA. In addition, amine and amino groups serve as HBDs. Consequently, predicting which compound will function as an HBD or HBA can be difficult. Therefore, for the purpose of this article and an easier understanding, we have labeled PEG as HBA and the other compounds as HBD. From the successfully formed *D*ES with PEG200, we selected seven HBDs that represent different chemical families and have favorable properties for cosmetic applications. These include lysine and proline (aliphatic and cyclic amino acids) and levulinic acid (linear carboxylic acid), which are used for skin conditioning; gallic acid (an aromatic carboxylic acid), which serves as an antioxidant, and glucose (sugar), sorbitol (sugar alcohol or polyol), and

Table 1
List of prepared *deep* eutectic solvents, along with their density and viscosity at 25 °C and 50 °C.

Name	HBA and HBD	Molar ratio	Water content (wt%)	Density (g cm^{-3})		Viscosity (mPa s)	
				T = 25 °C	T = 50 °C	T = 25 °C	T = 50 °C
PEG200-Lys-H_2O	Polyethylene glycol 200: L-lysine	2:1	20	1.1403	1.1220	92.34	25.79
PEG200-Pro-H_2O	Polyethylene glycol 200: L-proline	2:1	20	1.1429	1.1240	43.35	13.99
PEG600-Pro-H_2O	Polyethylene glycol 600: L-proline	2:1	20	1.1284	1.1079	87.77	26.34
PEG200-Sor-H_2O	Polyethylene glycol 200: D-sorbitol	2:1	20	1.1768	1.1580	62.59	17.53
PEG200-Glu-H_2O	Polyethylene glycol 200: D-glucose	2:1	20	1.1926	1.1741	83.67	21.87
PEG200-Gall.A	Polyethylene glycol 200: Gallic acid	2:1	0	1.2276	1.2085	1530.00	209.06
PEG200-Gall.A-H_2O	Polyethylene glycol 200: Gallic acid	2:1	20	1.1873	1.1691	85.96	22.73
PEG200-Lev.A	Polyethylene glycol 200: Levulinic acid	2:1	0	1.1291	1.1089	53.77	16.86
PEG200-Lev.A-H_2O	Polyethylene glycol 200: Levulinic acid	2:1	20	1.1168	1.0966	23.39	8.31
PEG600-Lev.A	Polyethylene glycol 600: Levulinic acid	2:1	0	1.1250	1.1046	136.98	42.20
PEG200-Urea	Polyethylene glycol 200: Urea	2:1	0	1.1534	1.1342	146.96	33.94
PEG200-Urea-H_2O	Polyethylene glycol 200: Urea	2:1	20	1.1331	1.1137	30.21	10.06
PEG600-Urea	Polyethylene glycol 600: Urea	2:1	0	1.1340	1.1140	228.94	61.46

urea, which are commonly used as humectants (Crowther, 2021; de Lima Cherubim et al., 2020; Mohan and Singh, 2020). PEG has also a versatile role in cosmetics, acting as an emulsifier, humectant, skin conditioner, solvent, thickening agent, and stabilizer (Jang et al., 2015). The selected compounds are GRAS compounds and/or ingredients accepted by the CIR, and have low environmental toxicity (Soni et al., 2020; Wawoczny and Gillner, 2023).

3.4. Experimental evaluation of DES as an extraction solvent

Initially, we investigated the performance of limonene extraction with *D*ES containing PEG200 and various HBDs, all formulated with 20 wt% water (Fig. 4A). Statistical analysis revealed that the extraction yields of *D*ES were significantly lower compared to the reference organic solvent heptane for all HBDs with 20 wt% of water, except for the *D*ES with levulinic acid (Table S5), indicating that PEG200-Lev.A-H_2O has comparable extraction yields to the reference while being a more sustainable alternative. PEG-200-Lev.A-H_2O also shows significantly higher extraction yields compared to other HBDs, making it the optimal choice for further optimization. When examining the impact of HBDs on extraction yields, no significant difference was observed between the amino acids proline and lysine. However, glucose was less effective than its related sugar alcohol, sorbitol, while among carboxylic acids, gallic acid was less effective than levulinic acid. Urea performed similarly well to sorbitol, but less efficiently than the amino acids and carboxylic acids.

Water addition can aid *D*ES formation and simultaneously improve its extractive performance by lowering the viscosity and enhancing mass transfer, but it also increases the system's polarity (Vilková et al., 2020), which can hinder the solubilization of highly hydrophobic compounds such as limonene. As predicted by COSMO-RS, more hydrophobic *D*ES, *i.e.* those prepared without added water (PEG200-Gall.A, PEG200-Lev.A, PEG200-urea), were expected to perform better, and indeed showed superior extraction efficiency. In detail, the water content had no effect on the extraction yield for PEG200-Lev.A, while PEG200-Gall.A and PEG200-urea showed significantly higher extraction yields in the absence of water (Table S6), with 1.4- and 2.9-fold increases, respectively (Fig. 4B). This confirms that water-free *D*ES are generally more effective for limonene extraction, which is consistent with COSMO-RS predictions. Consequently, higher water contents were not investigated, as further increases in system polarity would be unfavorable

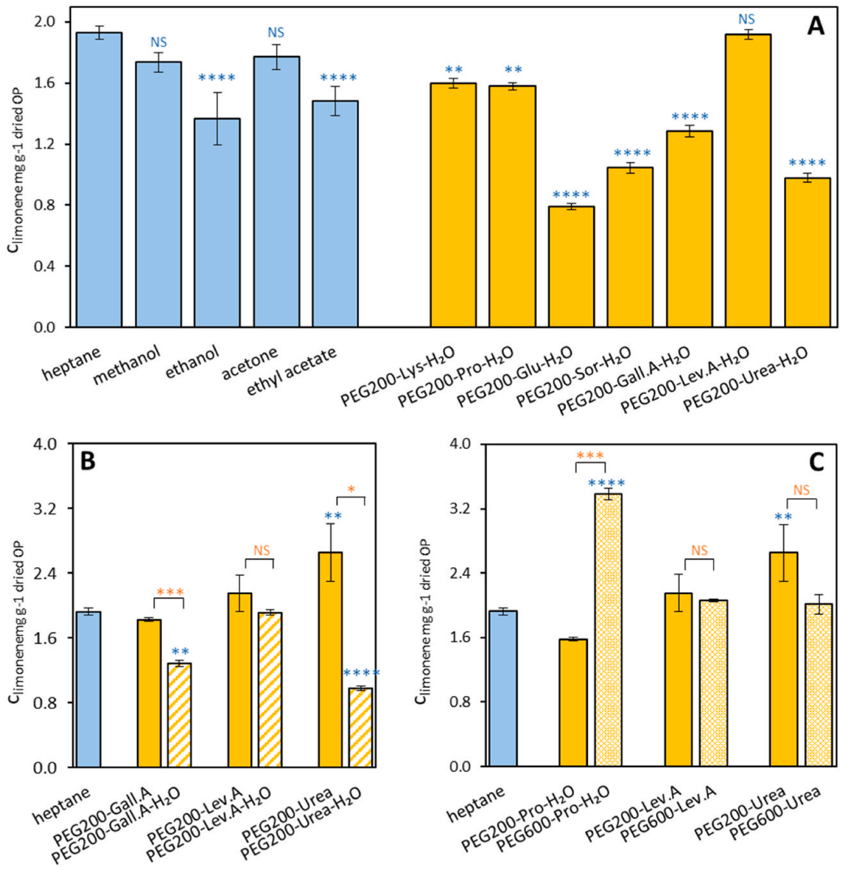

Fig. 4. Influence of solvent type on the extraction yield of limonene from dried orange peels: (A) comparison of different organic solvents and *D*ES with various HBDs, (B) effect to the water addition to the *D*ES, (C) influence of the PEG molecular weight on limonene extraction efficiency. Limonene yield is expressed as mg g^{-1} dried orange peel. The significance levels (NS $p \geq 0.05$, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$) in A are only shown for the comparison of each solvent with the reference solvent heptane; other statistical results are presented in Table S5. In B and C, the significance levels show the paired comparison made by the paired *t*-test for the respective solvent pair.

for the extraction of this highly hydrophobic compound.

A similar effect was observed by Panić et al. (2021) for choline chloride-based *D*ES, who reported a decrease in the extraction efficiency with higher water content (50–80 wt%) compared to 30 wt% water. However, this trend did not hold for *D*ES systems combining sugars and polyols (*e.g.*, glucose:fructose:sucrose, glucose:glycerol), suggesting a stronger interaction among components or synergistic effects between HBA and HBD. In contrast, Li et al. (2022) observed that choline chloride:propanediol (1:1) with 50 wt% water yielded the highest limonene extraction, while the anhydrous *D*ES performed worst. The authors attributed this to reduced viscosity enhancing diffusion. Moreover, the presence of water can accelerate limonene oxidation in the presence of oxygen and light (Li et al., 2018), which might explain their preference for hydrated systems and highlight differences with our findings.

To assess the influence of PEG molecular weight, we evaluated *D*ES based on PEG200 and PEG600, using the three most promising systems that offered a balance between extraction yield and the current cosmetic trend of using amino acids in formulations. Thus, PEG200-urea, PEG200-Lev.A, and PEG200-Pro-H_2O were selected (Fig. 4C). The PEG molecular weight had different effects depending on the HBD, with proline-based *D*ES showing a significantly higher extraction yield when PEG600 was used compared to PEG200. In contrast, the extraction efficiency of the HBDs levulinic acid and urea was not affected by PEG molecular weight (Table S7). PEG is usually considered a hydrophilic compound, but its unique properties also allow it to dissolve non-polar compounds. In general, lower molecular weight PEG is more hydrophilic, medium molecular weight PEG is more hydrophobic, and higher molecular weight PEG exhibits amphiphilic characteristics (Parray et al., 2020). The higher extraction yields of PEG600-Pro-H_2O compared to PEG200-Pro-H_2O suggest that *D*ES containing higher molecular weight PEG are slightly more hydrophobic, leading to improved limonene solubility and/or enhanced penetration into the biomass, facilitating limonene extraction from the oil vessels in orange peels. It is also worth noting that, while higher PEG molecular weight generally increases viscosity and may limit mass transfer, the observed extraction behavior suggests that solvent affinity and hydrophobic interactions play a more dominant role in limonene extraction under the conditions investigated. Unfortunately, *D*ES extracts containing proline were found to have a very unpleasant odor, which is not acceptable for use in cosmetic products. PEG600-Pro-H_2O would be a promising extraction solvent for applications where odor is not a problem, which is not the case for our intended application. In addition, the volume loss during the biomass separation step was up to 55 % for PEG200-Pro-H_2O, which is significantly higher compared to the solvent volume losses observed for other *D*ES (approximately 25 % volume loss for *D*ES containing lysine, levulinic acid, and urea; Table S8). This is possibly due to the swelling of the biomass as a result of interactions between the *D*ES and the biomass, which has been previously reported for lignocellulosic biomass pretreatment (Tian et al., 2020). However, high solvent losses represent a major drawback in industrial processes and should be minimized to reduce financial losses and solvent waste. Consequently, we had to exclude these proline-based *D*ES as a viable option for limonene extraction, as they are not suitable for direct use in cosmetic products.

In summary, the effect of PEG molecular weight on limonene extraction appears to be linked to two main factors. On one hand, increasing the PEG chain length generally reduces solvent polarity, which favors interactions with nonpolar compounds like limonene. On the other hand, changes in chain length also affect solvent viscosity and molecular flexibility, which in turn influences mass transfer and penetration into the biomass. For *D*ES based on proline, the use of PEG600 resulted in higher extraction yields, likely due to the formation of a more hydrophobic microenvironment, consistent with COSMO-RS predictions. However, in systems containing levulinic acid or urea, the difference between PEG200 and PEG600 was minimal, suggesting that solvent polarity alone does not fully explain the observed behavior. Instead, a combination of factors, including hydrogen bonding network, viscosity, and solute-solvent interactions, must be considered to fully understand and optimize extraction performance.

After carefully evaluating the influence of the HBD, water content, and PEG molecular weight, we identified the water-free *D*ES composed of urea and PEG200 as the most suitable system for limonene extraction from orange peels. This formulation delivered one of the highest extraction yields (second only to PEG600-Pro-H_2O) while also exhibiting lower viscosity than PEG600-Urea. Moreover, PEG200-urea forms a highly stable *D*ES due to its strong hydrogen bonding capacity (Chen et al., 2019), which is essential for ensuring the long-term stability of cosmetic products. Therefore, to further assess its suitability, a short-term stability study was conducted to determine which *D*ES are inherently stable and capable of protecting limonene from oxidation. Nevertheless, longer-term studies are recommended when these extracts are intended for direct application in cosmetic formulations.

3.5. *Stability of limonene extract in DES*

Limonene is prone to oxidation in the presence of light, oxygen, and/or water (Li et al., 2018). Its oxidation products (*e.g.* carvone, carveol, limonene oxide) tend to cause more allergic skin reactions than limonene itself (Ogueta et al., 2022), which could be a major limitation for cosmetic products. Therefore, it is important to provide a solvent that stabilizes limonene throughout the lifetime of the cosmetic product and prevents the oxidation process. *D*ES often have a high capacity to stabilize biomolecules compared to conventional solvents (Barbieri et al., 2020), which adds significant value when *D*ES remain in the final product. Thus, we investigated the stability of limonene by repeating the LLE step after five weeks with the extracts from orange peels stored in the dark at room temperature. We noticed that two *D*ES, *i.e.* PEG200-Glu-H_2O and PEG600-Urea, were not stable over this period due to precipitation or formation of crystal-like structures, making them unsuitable for use in cosmetic products. D-glucose predominantly exists in its cyclic form in aqueous solutions, making it likely that glucose self-association is stronger than its interaction with PEG, possibly due to the formation of a greater number of more favorable hydrogen bonds. The amount of PEG200 may not be sufficient to form hydrogen bonds for all available sugar molecules, leading to the formations of the observed structures (Hayyan et al., 2013). The remaining samples present more stable *D*ES formulations and show no significant decreases in limonene concentration after five weeks (Fig. 5, Table S9). The small variations observed in Fig. 5 are likely the result of analytical error and the variability in the LLE step (Table S10). In addition, no oxidation products of limonene (*i.e.* carvone, carveol or limonene oxide) were detected in any of the samples, confirming that PEG-based *D*ES maintain limonene stability over a five-week period (Fig. S4). Similarly, Kern et al. (2014) confirmed the stability of limonene in hydroalcoholic products over 9 months, whereas Li et al. (2018) observed a 13 % reduction in limonene concentration and the formation of oxidation products (limonene oxide, carveol, carvone, hydroperoxides, *etc.*) after just 40 h of exposure of pure limonene standard to UV radiation, air and high water content. Since there is no statistical evidence of a decrease in limonene concentration and the formation of oxidation products in our samples, we can conclude that the extracts are stable for at least 5 weeks in the dark and at room temperature, with the exception of PEG200-Glu-H_2O and PEG600-Urea *D*ES.

3.6. Extract characterization

Orange peels are primarily composed of carbohydrates (mainly cellulose, hemicellulose, and pectin), essential oils (predominantly limonene), flavonoids such as hesperidin and naringin as well as smaller amounts of proteins, lipids, and organic acids (Fontana, 2021; Revathi et al., 2025). Most of these bioactive compounds are considered safe for inclusion in cosmetic formulations, except when side effects may occur. This is the case with bergapten (5-methoxypsoralen), a natural furanocoumarin present in orange peel (Murador et al., 2019; Viñas-Ospino et al., 2022). Bergapten is a promising compound for medical applications due to its various pharmacological effects, including neuroprotection, organ protection, anticancer, anti-inflammatory, antimicrobial, and antidiabetic properties. However, its presence in cosmetic formulations is undesirable, as it increases the risk of skin cancer when exposed to light. Due to its phototoxicity, the International Fragrance Association limits the concentration of bergapten in cosmetic products to a maximum of 0.0015 % (which is equivalent to 15 μg mL^{-1}) (Burnett et al., 2021). Therefore, the presence of bergapten was investigated in detail, and it was not detected in any of the *D*ES extracts (Fig. S5), with concentrations remaining below the limit of detection (LOD = 0.08 μg mL^{-1}; Table S3), indicating that the extracts can be safely used in cosmetic formulations with respect to furanocoumarin content. Furthermore, potential oxidation products of limonene, particularly oxygenated monoterpenes such as linalool, limonene oxide, carvone, and carveol, were also investigated (Fig. S4). None of these compounds were detected, with concentrations below their respective limits of detection: linalool <15 μg mL^{-1}, limonene oxide <25 μg mL^{-1}, carveol <30 μg mL^{-1}, and carvone <20 μg mL^{-1} (Table S3). These results confirm the absence of detectable limonene oxidation during storage and highlight both the selectivity of the *D*ES systems studied and their stabilizing effect on limonene.

The σ-profiles and σ-potentials of limonene, linalool, limonene oxide, carvone, and carveol are shown in Fig. S2. This comparison clearly illustrates the differences in polarity and hydrogen-bonding behavior of these compounds, which in turn influence their solubility and interaction with the *D*ES. As aforementioned, limonene exhibits a narrow σ-profile centered around $\sigma \approx 0$ e nm^{-2}, confirming its highly nonpolar nature and lack of HBD or HBA functionality. In contrast, linalool and carveol, both containing hydroxyl groups, show prominent peaks at both $\sigma < -1$ e nm^{-2} and $\sigma > +1$ e nm^{-2}, reflecting their dual ability to participate in hydrogen bonding; linalool acting as both HBD and HBA due to its terminal alcohol, and carveol primarily as an HBD due to its secondary alcohol. Limonene oxide, despite being structurally similar to limonene, presents a largely nonpolar σ-profile with a modest peak at $\sigma > +1$ e nm^{-2}, corresponding to its epoxide ring acting as a weak HBA. Similarly, carvone, featuring a ketone group, has a strong HBA peak at $\sigma > +1$ e nm^{-2} consistent with the carbonyl oxygen's acceptor capability, while maintaining a nonpolar core. In this context and considering that the *D*ES under study are relatively hydrophobic, the selective extraction of limonene over the other terpenes was

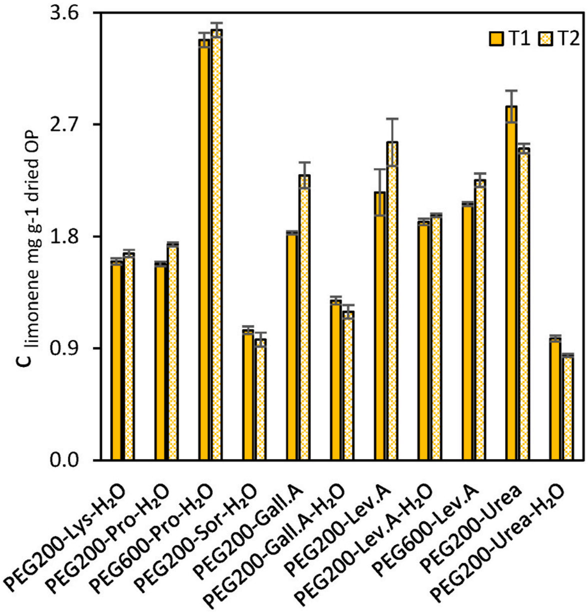

Fig. 5. Stability of limonene in extracts with *D*ES after 5 weeks of storing at the dark and at room temperature. Limonene concentration (mg g^{-1} dried orange peel) was measured immediately after extraction (T1) and after 5 weeks of storage at room temperature in the dark (T2).

expected (Ozturk and Gonzalez-Miquel, 2019; Panić et al., 2021).

At the same time, different flavonoids were also examined, specifically hesperidin, naringenin, quercetin, and epicatechin (Fig. 6 and Fig. S6). Among these, only hesperidin was detected in considerable amounts even after five weeks of storage, whereas the concentrations of naringenin, quercetin, and epicatechin remained below the limit of quantification (LOD, Table S3). Fig. 6 shows that the highest hesperidin yields were obtained using proline-based *D*ES; however, these solvents are unsuitable for cosmetic applications due to the aforementioned concerns. Therefore, the second-best *D*ES for hesperidin extraction is PEG200-Urea, which is also one of the best solvents for limonene extraction. It is also worth mentioning that the PEG200-Glu-H_2O and PEG600-Urea extracts could not be measured due to previously reported stability issues, and extracts containing gallic acid were not compatible with the mobile phases.

Flavonoids are highly valued in the cosmetic industry for their antioxidant, anti-inflammatory, antimutagenic, and anticarcinogenic properties. Hesperidin, in particular, has been shown to provide multiple skin benefits, including wound healing, UV protection, skin lightening, treatment of hyperpigmentation and depigmentation, anti-ageing effects, enhancement of the skin barrier, and management of various cutaneous diseases (Man et al., 2019; Rodrigues and Pintado, 2024). Research suggests that hesperidin is beneficial at concentrations ranging from 0.001 % to 10 % (Chen et al., 2017; Lai et al., 2024; Rodrigues and Pintado, 2024). Since the PEG200-Urea extract contained 2.7 mg mL^{-1} of hesperidin (24.3 mg g^{-1} orange peel), it is reasonable to assume that this concentration contributes both functional and stabilizing properties to the extract. Its antioxidant properties likely contribute to the stabilization of limonene in the extract, as evidenced by the absence of detectable degradation products. Combined with its UV-protective and anti-inflammatory effects, hesperidin enhances the overall functionality of the formulation, supporting its use as a multifunctional ingredient in cosmetics (Rodrigues and Pintado, 2024).

The concentration of hesperidin extracted using PEG200-Urea - 24.3 mg g^{-1} (or 2.7 mg mL^{-1}) - aligns well with values reported in the literature, where different extraction methods with organic solvents yielded hesperidin concentrations ranging from 0.01 to 70 mg g^{-1} (Figueira et al., 2023; Kalompatsios et al., 2024; Lachos-Perez et al., 2018; Lai et al., 2024; Luengo et al., 2013; Pereira et al., 2017). *D*ES have also been used for hesperidin extraction, with studies identifying ChCl:Glycerol (1:2) and ChCl:levulinic acid:N-methyl urea (1:1.2:0.8) as optimal solvents, achieving yields of 2.15 and 48 mg g^{-1}, respectively (de Oliveira et al., 2022; Gomez-Urios et al., 2024; Xu et al., 2019).

Comparing our biomass extracts with the existing literature is a challenge, as the differences are not only due to the extraction methods. Factors such as growing region, climatic conditions and orange variety can significantly influence the concentrations of bioactive compounds in oranges. In addition, differences in pre-treatment methods must be taken into account. For example, fresh biomass usually yields lower values (mg *per* g) than dried biomass due to its higher water content. These considerations are essential when evaluating the extraction performance of hesperidin and limonene compared to literature values. Nevertheless, it should be noted that the trends observed within the same study are likely to remain constant regardless of the biomass batches. Reported limonene concentrations extracted with hexane range from 6 to 27 mg g^{-1}, depending on the specific SLE procedures and orange varieties used (Battista et al., 2020; Ma et al., 2019; Ozturk et al., 2019; Panić et al., 2021). A few studies have also investigated limonene extraction with *D*ES, mainly based on ChCl in combination with sugars, polyalcohols, and carboxylic acids. Although the

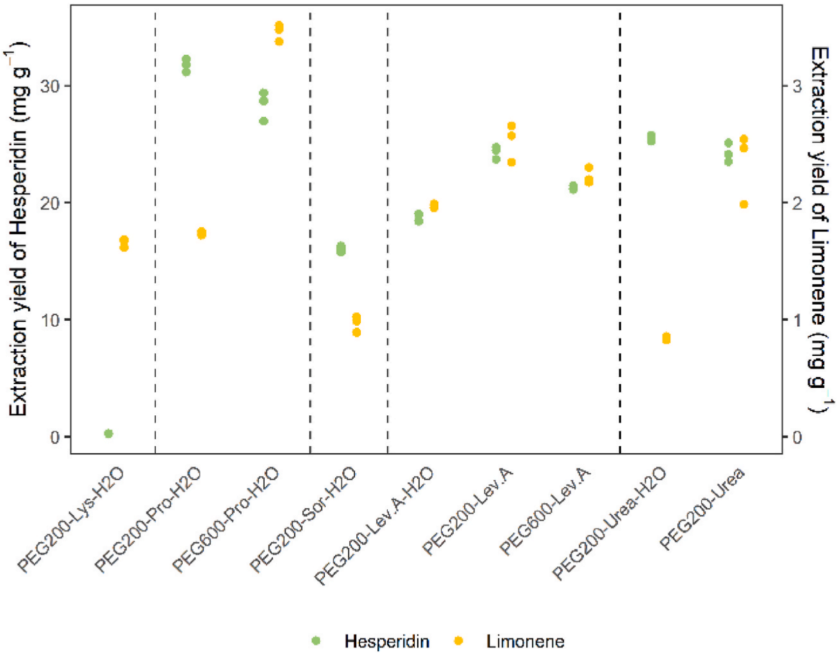

Fig. 6. Hesperidin and limonene concentration in *D*ES extracts after 5 weeks of storing at room temperature. Vertical dashed lines separate *D*ES groups according to the hydrogen-bond donor type.

reported extraction concentrations are higher than our results, *e.g.*, 3.7 mg g^{-1} (ChCl:glycerol, 1:2, 30 wt% water) and 17.8 mg g^{-1} (ChCl:propylene glycol:H_2O), their control extracts with hexane (6.4 and 26.7 mg g^{-1}, respectively) still outperformed the *D*ES extracts (Ma et al., 2019; Panić et al., 2021). In contrast, our optimal *D*ES (PEG200:Urea) achieved a 1.4-fold higher extraction yield compared to the control solvent, with values of 2.7 mg g^{-1} for PEG200-Urea and 1.9 mg g^{-1} for the heptane extract. Overall, PEG200-Urea not only outperforms the reference organic solvent in extracting limonene from orange peels but also enables the co-extraction of other valuable compounds for cosmetic formulations, such as hesperidin and *D*ES itself. Replacing organic solvents with *D*ES for biomass extraction is advantageous not only for achieving higher extraction yields, but also for promoting environmental sustainability and supporting a greener future. The selectivity of *D*ES toward limonene and co-extracted bioactive compounds is largely governed by solute-solvent affinity, polarity balance, and hydrogen bonding capabilities. For instance, the PEG200-urea system likely promotes better limonene solubilization through van der Waals interactions and reduced polarity, while simultaneously stabilizing hydrophilic flavonoids such as hesperidin through hydrogen bonding (Panić et al., 2021).

3.7. *Green assessment of the developed extraction process*

To evaluate and compare the sustainability of the extraction processes employing PEG200-urea as a *D*ES and heptane as a conventional organic solvent, the Path2Green software was applied. This methodology provides a structured yet flexible approach to quantify sustainability through a multi-criteria framework grounded in twelve guiding principles, enabling a comprehensive analysis of environmental, technical, and economic aspects of the processes. The formulation of the values used in this evaluation is based on these guiding principles, which are thoroughly detailed in the Path2Green metric. The output of the software is a dimensionless score ranging from −1.000 to +1.000, where +1.000 represents the ideal (most sustainable) process, 0.000 represents environmental parity with the reference process, and negative values denote lower sustainability performance (de Souza Mesquita et al., 2024).

The selection of raw material plays a pivotal role in sustainable extraction design. In this context, orange peel, an abundant agro-industrial byproduct, was chosen as the biomass source. Its renewable origin, wide availability, and status as a waste stream rendered it a highly favorable choice for both systems.

Logistics, often overlooked, represent a substantial portion of the environmental burden. By simulating a transport scenario with moderate distances (100 km), efficient road vehicles, and sustainable packaging, the analysis accounted for realistic conditions that moderately impacted the sustainability profile of each system. Regarding pre-treatment, both processes relied solely on mechanical grinding to enhance accessibility of target compounds, a minimal intervention that incurs negligible environmental costs. This approach aligns with the principle of reducing auxiliary steps to maintain process efficiency and mitigate energy use.

The nature of the solvent emerged as a critical differentiator. While the *D*ES is regarded as a benign and application-compatible medium, capable of being directly incorporated into final formulations, heptane, due to its toxicological profile, imposes restrictions and introduces additional downstream challenges. As such, the *D*ES provided a clear advantage in terms of process safety and regulatory alignment. Scalability considerations revealed that both extractions were conducted in batch mode, a configuration that, while flexible, offers limited economic competitiveness at larger scales. Consequently, their contribution to overall sustainability remained neutral in this regard.

Another point of divergence arises during purification. The *D*ES-based extract may, in specific applications, be used without further processing, given the compatibility of its components with cosmetic formulations. Heptane, on the other hand, necessitates complete removal due to its incompatibility with such applications, thereby introducing additional complexity and energy requirements. When analyzing extraction yield and biomass valorization, both systems demonstrated comparable performance, although exhaustive extraction was needed to maximize recovery. This led to a balanced assessment, neither favoring nor penalizing either strategy.

The post-treatment phase further emphasized the benefits of the *D*ES approach. Its inherent compatibility with formulation systems

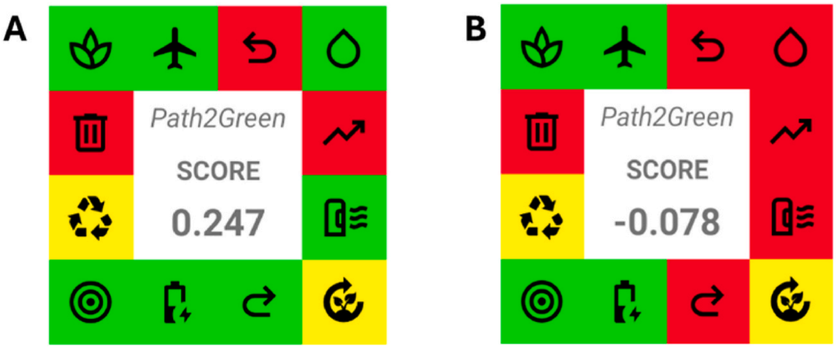

Fig. 7. Comparative environmental impact analysis of extraction processes using (a) *D*ES and (b) a heptane. The evaluation covers twelve principles: (I) biomass source, (II) transportation, (III) pre-treatment, (IV) solvent characteristics, (V) scale-up potential, (VI) purification, (VII) extraction yield, (VIII) post-treatment, (IX) energy consumption, (X) end-use application, (XI) potential for reuse or repurposing, and (XII) waste generation. Color indicators represent performance levels: green for favorable impact, yellow for areas needing improvement, and red for critical issues.

eliminated the need for solvent removal or further refinement, contrasting with the heptane process, which demands additional purification to meet safety standards, particularly in food and cosmetic contexts. Energy demands were modest for both methods, involving mild heating and agitation. However, the reliance on conventional (non-renewable) energy sources remains a common limitation in industrial practice, resulting in moderate sustainability scores for both.

In terms of applicability, the final products derived from both processes have potential uses in multiple domains, particularly in the pharmaceutical and cosmetic sectors. This versatility adds value and supports the broader viability of the extraction strategies. Moreover, both solvents allow for recovery and reuse, enabling the implementation of closed-loop operations that mitigate waste generation and improve resource efficiency, a key attribute in the pursuit of circular bioeconomy models. Nevertheless, the incomplete recovery of valuable compounds from the biomass left room for improvement in terms of waste minimization and full-spectrum valorization of the feedstock.

In summary, while both systems exhibited certain sustainable features, the *D*ES-based process consistently demonstrated superior performance across multiple dimensions, particularly in solvent safety, extract usability, and downstream simplicity. This was quantitatively reflected in the final sustainability scores: $+0.247$ for the *D*ES system, compared to -0.078 for heptane (Fig. 7). These results reinforce the growing recognition of *deep* eutectic solvents as promising alternatives in green extraction strategies, combining environmental compatibility with functional integration in end-use applications.

4. Conclusion

In this study, limonene was successfully extracted from orange peel waste using a more sustainable approach with *D*ES. Our results show that PEG200-urea achieved higher extraction yields than conventional organic solvents, which is an outcome that, to our knowledge, has not been reported before. Although the best-predicted *D*ES by COSMO-RS was not used due to challenges in its formation and cosmetic suitability, the performance of PEG200-urea highlights the potential of *D*ES as a safer and more environmentally friendly alternative to toxic organic solvents, as demonstrated using the Path2Green software. In addition to limonene, the process enabled the recovery of valuable co-products such as hesperidin, while avoiding the extraction of undesirable compounds, including bergapten and limonene degradation products. Consequently, the remaining biomass is suitable for bioethanol and biogas production, supporting a circular economy. By valorizing agricultural waste through sustainable extraction strategies, this work contributes to greener, more efficient processes with environmental and economic benefits.

CRediT authorship contribution statement

Monika Arnič: Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Kristina Andrejc:** Writing – original draft, Validation, Investigation, Formal analysis, Data curation. **Mónia A.R. Martins:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Filipe H.B. Sosa:** Writing – original draft, Validation, Investigation, Funding acquisition, Data curation. **João A.P. Coutinho:** Writing – review & editing, Visualization, Software, Funding acquisition. **Blaž Likozar:** Writing – review & editing, Resources, Funding acquisition. **Filipa A. Vicente:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scp.2026.102339.

Data availability

Data will be made available on request.

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