

Extraction of Mangiferin from Mango Leaves Using Ethanol–Water–Liquid CO₂ Mixed Solvents and Hansen Solubility Parameter Analysis

Toshihiro TAKESHITA¹, Tanjina SHARMIN², Minami KANAZAWA², Atsuki NISHIHARA², Haruka OKUMOTO², Kazusa MISHIMA³, Sahena FERDOSH⁴, Salim MUSTOFA⁵, Keiichi IRIE⁶, Tomomitsu SATHO⁶, Mikio OUCHI², Hussein ZNAD⁷, Agus SAPTORO⁸ and Kenji MISHIMA^{1*}

¹Department of Resource Circulation and Environmental Engineering, Graduate School of Engineering, Fukuoka University, 8-19-1 Nanakuma, Jonan-ku Fukuoka 814-0180, Japan; ²Department of Chemical Engineering, Faculty of Engineering, Fukuoka University, 8-19-1 Nanakuma, Jonan-ku Fukuoka 814-0180, Japan; ³Department of Pharmacy, Tsukuba University Hospital, 2-1-1 Amakubo, Tsukuba, Ibaraki 305-8576, Japan; ⁴College of Natural and Applied Sciences, Western Pacific Tropical Research Center, University of Guam, 303 University Drive, Mangilao, Guam 96913, USA; ⁵Center for Science and Technology of Advanced Materials, Indonesia Nuclear Energy Agency, Serpong, Tangerang Selatan 15314, Indonesia; ⁶Faculty of Pharmaceutical Sciences, Fukuoka University, 8-19-1 Nanakuma, Jonan-ku Fukuoka 814-0180, Japan; ⁷Western Australian School of Mines: Minerals, Energy and Chemical Engineering, Faculty of Science and Engineering, Curtin University, Australia; ⁸Department of Chemical Engineering, Faculty of Engineering, Curtin University, Australia

* Corresponding author: mishima@fukuoka-u.ac.jp

(Received December 26, 2025; Accepted March 18, 2026)

Mangiferin is a bioactive polyphenol abundant in mango (*Mangifera indica* L.) leaves and exhibits notable antidiabetic and antioxidant activities. In this study, a green extraction system based on ethanol, water, and liquid carbon dioxide (CO₂) was developed to enhance mangiferin extraction. Experiments were conducted in a 50 cm³ high-pressure cell at 25 °C and 8 MPa using ethanol–water mixtures with varying volume fractions with and without liquid CO₂. The highest extraction yield was obtained at an ethanol volume fraction of 25% in the binary ethanol–water system, consistent with the strong hydrogen-bonding affinity of mangiferin. The addition of liquid CO₂ improved solvent permeability and mass transfer, leading to a further exponential increase in extraction yield. A thermodynamic correlation model based on Hansen solubility parameters produced significant errors at high ethanol concentrations but quantitatively described the exponential increase in yield due to CO₂ addition across a wide composition range with high extraction rates.

1. Introduction

Mango (*Mangifera indica* L.) leaves are rich in a variety of antioxidant compounds, including mangiferin, phenolic acids, benzophenones, flavonoids, ascorbic acid, carotenoids, and tocopherols [1-3]. Among these constituents, mangiferin, a C-glucosyl xanthone, has received significant attention due to its antidiabetic, anti-inflammatory, anticancer, and anti-allergic activities [4-6]. The chemical structure of mangiferin is shown in Figure 1. Because mango leaves are an abundant agricultural byproduct, they



Copyright © 2026 Japan Association of Solvent Extraction. This is an open access article distributed under the terms of Creative Commons Attribution License (CC BY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original source is properly credited.

represent a promising and sustainable source of mangiferin for functional foods and pharmaceutical applications.

Conventional extraction methods for mangiferin commonly employ organic solvents such as methanol and acetone [7,8]. However, these solvents pose environmental and health concerns, motivating the development of greener extraction technologies. Carbon dioxide (CO₂) is an attractive alternative solvent because of its low toxicity, chemical inertness, and ease of removal. Nevertheless, due to its nonpolar nature, CO₂ alone is insufficient for extracting highly polar compounds such as mangiferin [9].

To address this limitation, polar co-solvents such as ethanol and water have been introduced to enhance solvent polarity and hydrogen-bonding capacity [10-12]. Ethanol–water mixtures are particularly attractive because both solvents are food-grade and environmentally benign. Despite extensive studies on the supercritical and liquid CO₂ extraction of plant materials, reports focusing on mangiferin extraction from mango leaves using mixed green solvents remain scarce.

In addition, predictive models for extraction yield are essential for rational process design. Hansen solubility parameters (HSP) have been widely applied to describe solute–solvent affinity in polymer science and extraction processes [13-15]. In this study, ethanol, water, and liquid CO₂ were employed as green solvents to extract mangiferin from mango leaves. Furthermore, a simple thermodynamic model based on HSP was developed to correlate solvent composition with extraction yield.

2. Experimental

2.1 Reagents

Fresh mango leaves were collected, washed with distilled water, and air-dried under ambient conditions (25 °C). The dried leaves were then ground and sieved to obtain particles with a size of approximately 1 – 2 mm prior to extraction. The residual moisture content of the air-dried plant materials was expected to be within the range of approximately 5 – 10 wt% under ambient conditions. All samples were prepared under the same drying and grinding conditions to ensure consistency and reproducibility. Analytical-grade ethanol (> 99.7 wt%, Wako Pure Chemical Industries Ltd.) and distilled water were used as solvents without further purification in the conventional liquid extraction and the high-performance liquid chromatography (HPLC). High-purity CO₂ (> 99%, Fukuoka Sanso Co., Ltd., Fukuoka, Japan) was used as liquid CO₂ without further purification. A mangiferin standard (> 97 wt%, Sigma-Aldrich Co., Japan) was used as received for quantitative analysis.

2.2 Experimental setup

A schematic diagram of the experimental apparatus used for liquid CO₂ extraction is shown in Figure 2. A detailed description of the apparatus is given elsewhere [10,11]. In brief, the apparatus was equipped with two extraction cells: one with a volume of approximately 150 cm³ (34 mm i.d., 165 mm long, Toyo Koatsu Co., Ltd., Hiroshima, Japan) and one with a volume of approximately 50 cm³ (34 mm i.d., 76 mm long, JASCO, Tokyo, Japan). Liquid CO₂ from a gas cylinder was fed through a line passing via the dryer

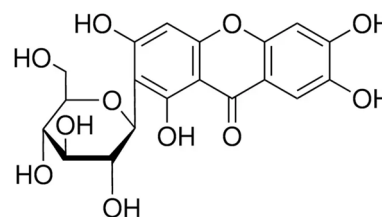


Figure 1. Structure of mangiferin.

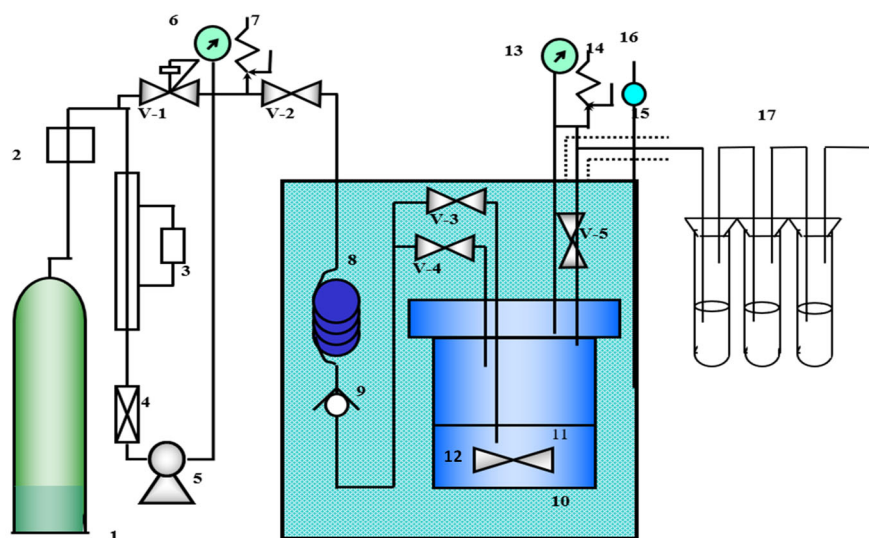


Figure 2. Schematic diagram of the experimental apparatus used for liquid CO₂ extraction experiments with ultrasonic irradiation; 1: gas cylinder, 2: dryer, 3: cooling unit, 4: filter, 5: HPLC pump, 6: pressure gauge, 7: safety valve, 8: pre-heater, 9: check valve, 10: water bath, 11: extraction cell, 12: stirrer, 13: pressure gauge, 14: safety valve, 15: heater, 16: thermocouple, 17: cold traps, V-1 and V-6: backpressure regulators, V-2 to V-5: stop valves.

and cooling unit to an HPLC pump (SCF-Get, JASCO, Tokyo, Japan), where it was further pressurized to the desired extraction pressure and finally sent into the extraction cell. Cooling at the pump head was necessary to maintain the CO₂ in its liquid state. The extraction cell was heated to the desired extraction temperature by immersing it in a water bath controlled to within ± 0.1 °C of the extraction temperature. The pressure of the extraction cell was controlled to within ± 0.3 MPa of the desired pressure by a backpressure regulator (880-81, JASCO, Tokyo, Japan) located at the outlet of the cell. The temperature of the extraction cell was measured using a thermocouple located inside the cell.

2.3 Extraction experiments

2.3.1 Conventional aqueous ethanol extraction

Conventional aqueous ethanol extraction of mangiferin from 0.3 g of mango leaf powder was performed using ethanol–water solutions with ethanol concentrations ranging from 0 to 100% (v/v) at 25 °C and atmospheric pressure. Extraction was conducted using a water bath (Eyela SB-24, Tokyo Rikakikai Co., Ltd.) with a shaker (Eyela SS-8) and a thermostatic circulator (Eyela T-80) set to 25 ± 0.1 °C. A sample was taken 1 h after the start of the extraction and was quantitatively analyzed for mangiferin by HPLC.

2.3.2 Aqueous ethanol extraction with liquid CO₂ as a co-solvent

Aqueous ethanol extraction with liquid CO₂ as a co-solvent was carried out using the same mango leaf powder (0.3 g) and different ethanol–water solvent compositions (Table 1). The extraction was conducted in a high-pressure extraction vessel with a total internal volume of 50 mL. The mango leaf powder was placed in the vessel, followed by 34 or 42 mL of the ethanol–water solution. The vessel was then pressurized with liquid CO₂ to 8 MPa at 25 °C. After reaching the target pressure, extraction was performed for 1 h under

static conditions with the extraction temperature controlled at 25 ± 0.1 °C using a thermostatic circulator. The high-pressure vessel was then gradually depressurized to atmospheric pressure, and the liquid extract was recovered. The released CO₂ gas was quantified using a wet gas flow meter to determine the total CO₂ volume under ambient conditions. The extract was filtered and subsequently quantitatively analyzed for mangiferin by HPLC.

Table 1. Extraction solvent compositions with or without liquid CO₂.

Experiment number	Composition			V [mL]
	$\phi(\text{EtOH})$	$\phi(\text{H}_2\text{O})$	$\phi(\text{CO}_2)$	
1	0	1	0	30
2	0.25	0.75	0	30
3	0.5	0.5	0	30
4	0.75	0.25	0	30
5	1	0	0	30
6	0.698	0.219	0.083	44
7	0.63	0.21	0.16	42
8	0.51	0.17	0.32	34
9	0.42	0.42	0.16	42
10	0.24	0.24	0.52	12
11	0.21	0.63	0.16	42
12	0.17	0.51	0.32	34

V [mL]: total volume of ethanol and water placed inside the experimental cell.

2.4 Analysis

Qualitative and quantitative analysis of the liquid extract was conducted by High-performance liquid chromatography (HPLC) using a modified version of a reported method [10,11]. The HPLC analysis was conducted using a TSK-GEL column (ODS-80TS, Tosoh Co., Tokyo, Japan) with dimensions of 150×4.6 mm, a column oven set at 40 °C, and a UV detector (875-UV, JASCO, Tokyo, Japan) with the wavelength set at 315 nm. Two mobile phases were used for the HPLC analysis—HPLC-grade methanol and 0.1% acetic acid in water—where the methanol gradient profile is shown in Table 2. The total flow rate of the mobile phase was set at 1.0 mL/min.

Table 2. Time course of the methanol gradient for HPLC analysis.

Time [min]	0	25	40	50	60	65	75
Methanol [vol%]	5	40	60	90	90	5	5

Concentrations of mangiferin in the liquid extracts were calculated using a calibration curve constructed from mangiferin standard solutions with known concentrations. The extraction yield of mangiferin was evaluated as milligrams of mangiferin per gram of dry mango leaf powder. The yield (Y_{yield}) was calculated using the following equation:

$$Y_{\text{yield}} = \frac{\text{Amount of CGA or rutin in extract [mg]}}{\text{Dry peel powder [mg]}} \quad (1)$$

3. Results and Discussion

3.1 Identification of compounds in aqueous ethanol extraction and aqueous ethanol extraction with CO₂ entrainer

HPLC chromatograms of the mango leaf extracts obtained from aqueous ethanol extraction are shown in Figure 3a. The major component (mangiferin, peak at 27 min) was confirmed by analysis of the standard solution (Figure 3b), which exhibited the same retention time.

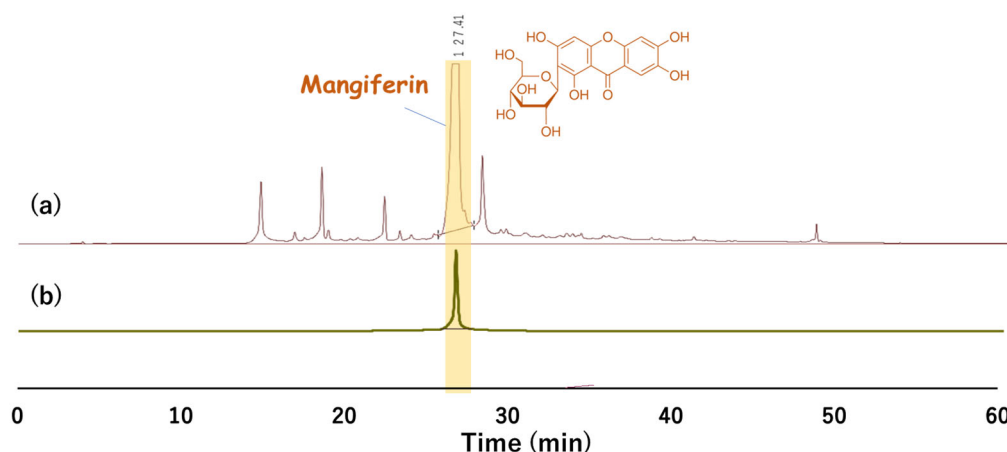


Figure 3. HPLC chromatogram profile of extracts obtained from mango leaf extraction: (a) aqueous ethanol extraction at 25 °C and atmospheric pressure for 60 min ($\phi_{\text{EtOH}} = 0.25$) and (b) standard solution.

3.2 Effect of ethanol–water composition on mangiferin yield

Figure 4 shows the extraction yield of mangiferin obtained by conventional solid–liquid extraction at 25 °C and atmospheric pressure as a function of the ethanol–water composition. Ethanol volume fractions ($\phi_1 = \text{EtOH}$) of 0 and 1 correspond to pure water and pure ethanol, respectively. The extraction yields obtained using pure water and pure ethanol were 75.9 and 24.3 mg g⁻¹ dry leaves, respectively. The extraction yield of mangiferin exhibited a maximum at $\phi_1 = 0.25$, followed by a gradual decrease with further increases in ethanol fraction. This nonlinear behavior indicates that the solvent composition, rather than the water content alone, governs the extraction efficiency of mangiferin.

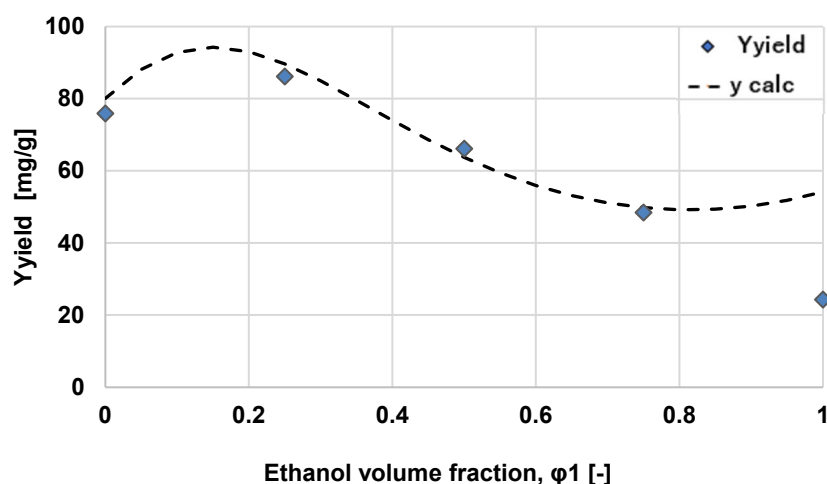


Figure 4. Extraction yield of mangiferin obtained by conventional solid–liquid extraction at 25 °C and atmospheric pressure as a function of the ethanol volume fraction (ϕ_1 = EtOH). The calculated values were obtained using the model of Hansen solubility parameters.

Mangiferin is a xanthone C-glycoside containing multiple hydroxyl groups and a sugar moiety, giving it relatively high polarity and strong hydrogen-bonding capacity. At intermediate ethanol–water compositions, the mixed solvent provides an optimal polarity environment in which hydrogen-bonding interactions from water coexist with the enhanced organic solvation capacity of ethanol. As a result, solute–solvent affinity and mass transfer from the plant matrix are maximized. A similar enhancement at intermediate ethanol fractions has been reported for polar phenolic compounds such as mangiferin, with maximum extraction yields typically observed at ethanol mole fraction $x_{\text{EtOH}} \approx 0.13 - 0.25$ [16–18].

These results indicate that solvent polarity and solute–solvent affinity play a decisive role in mangiferin extraction, suggesting that further modulation of the solvent properties – such as through the introduction of pressurized CO_2 – may significantly influence extraction performance.

3.3 Effect of liquid CO_2 as a co-solvent on mangiferin yield

Using the optimal ethanol–water composition identified in Section 3.2, the effect of introducing CO_2 as a co-solvent was examined to further modify the solvent properties and extraction efficiency. Figure 5 shows the effect of CO_2 addition on the extraction yield of mangiferin (Y_{yield}) when CO_2 is added to the solvent at different volume fraction ratios of ethanol to water ($\phi_1:\phi_2 = 3:1, 1:1, 1:3$) in CO_2 –EtOH– H_2O mixed solvents at 25 °C and 8 MPa.

Compared with the corresponding EtOH– H_2O system in the absence of CO_2 , the addition of liquid CO_2 led to a noticeable improvement in extraction performance that depended on the volume fraction ratio of ethanol to water. The liquid CO_2 improved solvent permeability and mass transfer, leading to an exponential increase in extraction yield. Regarding the volume fraction of CO_2 , the fact that the extraction yield y increases exponentially indicates that the CO_2 volume fraction plays a significant role and should be incorporated into thermodynamic models of extraction yield. Notably, for the ethanol-rich system ($\phi_1:\phi_2 = 3:1$), the extraction yield increased markedly with increasing CO_2 fraction, showing a strong positive

dependence. A similar but more moderate enhancement was observed for the equimolar system (1:1). In contrast, for the water-rich system (1:3), the effect of CO₂ addition was less pronounced and did not show a consistent increasing trend.

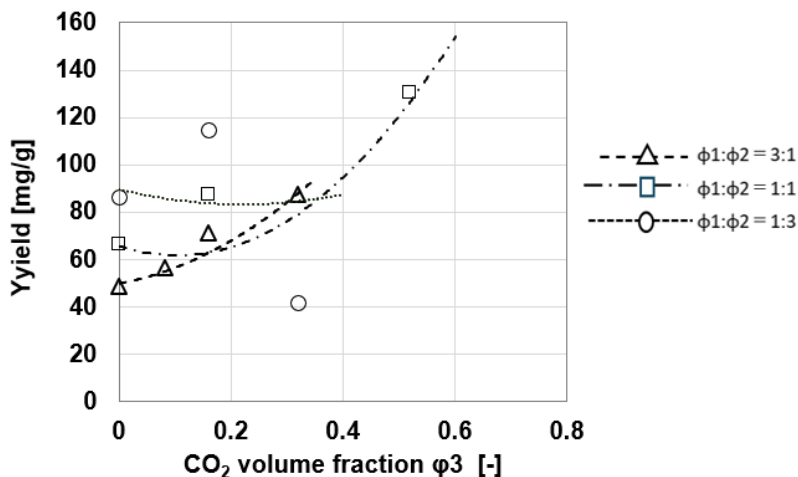


Figure 5. Effect of CO₂ addition on extraction yield of mangiferin, Y_{yield} when CO₂ is added to a solvent with a constant ratio of volume fraction of ethanol to water ($\phi_1:\phi_2=3:1, 1:1, 1:3$) in CO₂–EtOH–H₂O mixed solvents at 25 °C and 8 MPa

These results indicate that CO₂ acts as an effective co-solvent, particularly in ethanol-rich environments, where it forms CO₂-expanded liquid phases. This expansion reduces solvent viscosity and enhances diffusivity, facilitating improved extraction efficiency. Furthermore, the controlled reduction in solvent polarity appears to remain compatible with mangiferin solubility under ethanol-rich conditions, leading to enhanced yield. In contrast, in water-rich systems, the limited solubility of CO₂ and limited formation of expanded phases reduce its impact on extraction performance.

Overall, the role of CO₂ is strongly dependent on the initial solvent composition, with the most significant enhancement observed at higher ethanol fractions. This highlights the importance of solvent composition in optimizing CO₂-assisted extraction systems.

To quantitatively explain the observed solvent–solute compatibility in both CO₂-free and CO₂-assisted systems, HSP analysis was conducted, as discussed in the following section.

3.4 Liquid equilibrium behavior of the CO₂–ethanol–water system

To interpret the extraction behavior of mangiferin, it is essential to clarify the phase behavior of the CO₂–ethanol–water solvent system. This ternary system may exist either as a single homogeneous phase or as two coexisting phases depending on temperature, pressure, and solvent composition. Phase transitions strongly influence solvent polarity, solute partitioning, and mass-transfer characteristics, thereby affecting extraction efficiency. In this study, solvent compositions forming a two-phase system that facilitates solute recovery were selected. The non-random two-liquid (NRTL) model and Peng–Robinson equation of state (PR-EOS) were employed to predict phase separation behavior [19,20].

Vapor–liquid equilibrium (VLE) calculations were performed for the CO₂–EtOH–H₂O system at 298.15 K and 8.0 MPa to provide a thermodynamic basis for the experimentally observed extraction trends. Phase equilibrium was described using a γ – ϕ approach, in which the vapor phase was modeled using the PR-EOS combined with the Wong–Sandler/Huron–Vidal (WS/HV) mixing rule, while liquid-phase non-ideality was represented using the NRTL activity-coefficient model. This formulation ensured thermodynamic consistency between the vapor- and liquid-phase descriptions [21-23].

The system consisted of ethanol (component 1), water (component 2), and CO₂ (component 3) at 298.15 K and 8.0 MPa. At VLE, the fugacity of each component is equal in both phases, as follows:

$$f_i^V(T, P, y) = f_i^L(T, P, x) \quad (i = 1, 2, 3) \quad (2)$$

The vapor-phase fugacity is expressed as

$$f_i^V = y_i \phi_i(T, P, y) P \quad (3)$$

where y_i is the vapor-phase mole fraction and ϕ_i is the fugacity coefficient obtained from the PR-EOS combined with the WS/HV mixing rule.

Because CO₂ is subcritical at 298.15 K, different reference states were adopted for CO₂ and for the solvent components. The liquid-phase fugacity of CO₂ was expressed using Henry's law:

$$f_3^L = x_3 \gamma_3^{NRTL} H_3(T) \quad (4)$$

where H_a is the Henry constant of CO₂ in the solvent. For ethanol and water, pure-component vapor pressure reference states were applied:

$$f_i^L = x_i \gamma_i^{NRTL} P_i^{sat}(T) \exp \left[\frac{V_i^L (P - P_i^{sat})}{RT} \right] \quad (i = 1, 2) \quad (5)$$

Under the conditions studied, the Poynting correction term was small and therefore approximated as unity.

Liquid-phase non-ideality was described using the NRTL model, with activity coefficients calculated from the standard three-component formulation involving binary interaction parameters τ_{ij} and non-randomness factors α_{ij} (Table 3). Representative binary interaction parameters were adopted for the EtOH–H₂O, CO₂–EtOH, and CO₂–H₂O pairs, while ternary interaction parameters were neglected.

$$\ln \gamma_i = \sum_{j=1}^3 \frac{x_j \tau_{ji} G_{ji}}{\sum_{k=1}^3 x_k G_{jk}} + \sum_{j=1}^3 \frac{x_j G_{ji}}{\sum_{k=1}^3 x_k G_{jk}} \left(\tau_{ij} - \frac{\sum_{m=1}^3 x_m \tau_{mj} G_{mj}}{\sum_{m=1}^3 x_m G_{mk}} \right) \quad (6)$$

$$G_{ji} = \exp(\alpha_{ij} \tau_{ij}) \quad (7)$$

Table 3. Binary NRTL parameters (representative values) [20,24].

Pair	τ_{ij}	τ_{ji}	α_{ij}
EtOH–H ₂ O	1.7	0.3	0.3
CO ₂ –EtOH	0.9	1.6	0.3
CO ₂ –H ₂ O	1.8	2.5	0.3

The vapor phase was described using the PR-EOS combined with the WS/HV mixing rule [19,20]. Pure-component PR parameters were calculated from critical properties and acentric factors according to the standard PR formulation. The attractive and co-volume parameters for component i were defined as:

$$a_i = 0.45724 \frac{R_2 T_{ci}^2}{P_{ci}} \alpha_i \quad (8)$$

$$b_i = 0.07789 \frac{RT_{ci}}{P_{ci}} \quad (9)$$

where the temperature dependence of the attraction term is given by

$$\alpha_i = \left[1 + \kappa (1 - \sqrt{T / T_{ci}}) \right]^2 \quad (10)$$

and

$$\kappa_i = 0.37464 + 1.5422\omega_i - 0.26992\omega_i^2 \quad (11)$$

Here, T_{ci} , P_{ci} , and ω_i denote the critical temperature, critical pressure, and acentric factor of component i , respectively. The critical properties and acentric factors of CO₂, ethanol, and water used in this study are summarized in Table 4.

Table 4. Critical properties and acentric factors of ethanol, water, and CO₂ [21].

Component	T_c [K]	P_c [MPa]	Ω
EtOH	514.0	6.137	0.644
H ₂ O	647.10	22.064	0.344
CO ₂	304.13	7.377	0.224

To ensure thermodynamic consistency between the equation of state and the excess Gibbs energy description of the liquid phase, the WS/HV mixing rule was applied. The mixture co-volume parameter was calculated as:

$$b_{mix} = \sum_i y_i b_i \quad (12)$$

and the mixture attraction parameter was expressed as

$$a_{mix} = \sum_i \sum_j y_i y_j \sqrt{a_i a_j} - \frac{RT}{P} \left(\sum_i x_i \ln \gamma_i \right) \frac{b_{mix}}{b_0} \quad (b_0 = b_{mix}) \quad (13)$$

This formulation explicitly incorporates the liquid-phase excess Gibbs energy through the activity coefficients obtained from the NRTL model, thereby ensuring consistency between the vapor- and liquid-phase thermodynamic descriptions.

The fugacity coefficient of component i in the vapor phase was calculated using the standard PR expression:

$$\ln \phi_i = \frac{b_i}{b_{mix}} (Z - 1) - \ln(Z - B) - \frac{A}{2\sqrt{2}B} \left(\frac{2 \sum_j y_j a_{ij}}{a_{mix}} - \frac{b_i}{b_{mix}} \right) \ln \left(\frac{Z + (1 + \sqrt{2})B}{Z + (1 - \sqrt{2})B} \right) \quad (14)$$

where Z is the compressibility factor and A and B are the reduced PR parameters.

Henry constants and vapor pressures at 298.15 K were taken from the literature. The Henry constants of CO₂ in water and ethanol were 3.4×10^9 Pa and 1.5×10^8 Pa, respectively. The vapor pressures of ethanol and water were 7.83×10^3 Pa and 3.17×10^3 Pa, respectively. For mixed ethanol–water solvents, the effective Henry constant of CO₂ was approximated using a reciprocal linear mixing rule:

$$\frac{1}{H_3^{mix}} = \frac{x_1}{H_{3,EtOH}} + \frac{x_2}{H_{3,H_2O}} \quad (15)$$

This approximation is widely employed in engineering calculations and provides a reasonable representation of CO₂ solubility in mixed solvent systems relevant to extraction processes. In this study, the VLE analysis revealed that at intermediate ethanol fractions, the CO₂–EtOH–H₂O system favors expanded single-liquid-phase regions with moderate polarity, which are conducive to mangiferin solubilization and mass transfer. In contrast, at high ethanol fractions, CO₂ addition significantly reduces solvent polarity and may induce phase separation, limiting effective solvent–solute contact. These thermodynamic effects explain the deviations observed between experimentally measured extraction yields (Y) and Hansen-based predicted yields (Y_{calc}).

Overall, the phase equilibrium behavior of the CO₂–EtOH–H₂O system provides a macroscopic thermodynamic framework that complements the molecular-level solvent–solute affinity described by HSP. The phase diagram in Figure 6 indicates that the composition used in this extraction experiment is a two-phase system. During the extraction experiment, we also confirmed the formation of a gas–liquid two-phase system in the high-pressure cell equipped with observation windows.

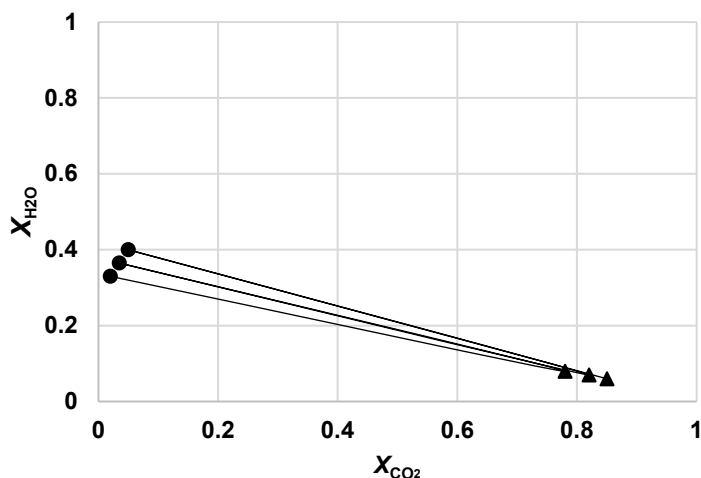


Figure 6. Tie lines of ternary VLE composition of the CO₂–EtOH–H₂O system (298.15 K, 8 MPa).

3.5 Thermodynamic model for extraction prediction using Hansen solubility parameters

The extraction behavior of mangiferin in mixed CO₂–ethanol–water media was predicted using a thermodynamic model incorporating HSP [13]. In this study, CO₂ was treated as a liquid in the HSP calculation. HSP can be used to predict the solubility S in solvents. Since the extraction yield Y_{yield} strongly

depends on the solubility of the solute in the extraction solvent, it was assumed that the extraction yield could be expressed with HSP representing solubility. The model assumes that the solubility of a solute in a given solvent is governed by the difference in cohesive energy densities between them, expressed as the Hansen three-dimensional interaction space consisting of dispersion (δ_D), polar (δ_P), and hydrogen-bonding (δ_H) contributions. For a solute (s) and solvent (v or mix), the Hansen interaction radius is defined as:

$$R_a^2 = 4(\delta_{D,mix} - \delta_{D,s})^2 + (\delta_{P,mix} - \delta_{P,s})^2 + (\delta_{H,mix} - \delta_{H,s})^2 \quad (16)$$

A smaller R_a reflects better affinity, whereas a larger R_a indicates decreasing solubility.

For mixed solvents, the HSP components were calculated assuming ideal volume additivity:

$$\delta_{k,mix} = \sum_i \phi_i \delta_{k,i} \quad (k = D, P, H) \quad (17)$$

where ϕ_i is the volume fraction of each solvent component (i = ethanol, water, CO₂) in the mixed solvents.

Based on regular-solution theory, the Gibbs free energy of dissolution increases proportionally with R_a^2 . Therefore, we assumed that the logarithmic form of the extraction yield (Y_{yield}) at a fixed temperature could be expressed as follows:

$$\ln Y_{yield} = a_0 + a_1 R_a^2 + a_2 R_a^4 + a_3 \phi_3 \quad (18)$$

where a_0 , a_1 , a_2 , and a_3 are temperature-dependent regression parameters. Thermodynamically, the logarithm of Y_{yield} should be approximated by a linear function of R_a^2 . However, to expand the applicability of HSP and gain insights useful for industrial extraction, the model was extended to include a quadratic term of R_a . The effect of adding CO₂ as an entrainer was assumed to be proportional to its volume mole fraction in the solution. These parameters were determined by parameter fitting using all experimental data to minimize the error between the experimental and calculated values of Y_{yield} . Using the determined parameters, the extraction yield Y_{yield} of mangiferin at 25 °C for each extraction operation can be calculated using HSP by providing the solvent composition according to the following equation.

$$Y_{calc} = \exp \left[a_0 + a_1 R_a^2(s, mix) + a_2 R_a^4(s, mix) + a_3 \phi_3 \right] \quad (19)$$

Table 5 shows the HSP for the solute and each solvent used in this study.

Table 5. HSP for the solute and each solvent [13].

Substance	δ_D	δ_P	δ_H
Ethanol	15.8	8.8	19.4
H ₂ O	15.5	16	42.3
CO ₂	15.7	6.3	5.7
Mangiferin	21.4	11.5	23.5

The parameters of the optimized eq. (19), derived from the extraction rate data and the HSP calculated from each composition, were as follows:

$$a_0 = 3.0639, \quad a_1 = 0.00770, \quad a_2 = -1.02 \times 10^{-5}, \quad a_3 = 1.44$$

The yields calculated using these parameters are shown as lines in Figures 4 and 5. In the ethanol–water mixed solvent system, the HSP model produced significant errors at high ethanol fractions ($\phi_1 > 0.75$), particularly at $\phi_1 = 1.0$ (Figure 4). Therefore, caution should be exercised when applying eq. (19) across a wide range of solvent compositions. However, at lower ethanol volume fractions ($\phi_1 = 0$ to 0.75), the HSP model adequately described the extraction trend. As shown in Figure 5, at ethanol volume fractions of $\phi_1 = 0.24$ to 0.69 , adding a small amount of CO_2 resulted in an exponential increase in the extraction yield at each constant ethanol-to-water volume fraction ratio ($\phi_1:\phi_2 = 3:1, 1:1$) in CO_2 –EtOH– H_2O mixed solvents at 25°C and 8 MPa . The model appears to be more reliable within a limited concentration range, particularly in aqueous systems with a low to moderate ethanol concentration. Nevertheless, this study demonstrates the potential applicability of HSP, which are derived solely from molecular structures, for describing trends in solvent extraction systems. Table 6 shows the correlation results along with their error margins. The overall average deviation is 25.1%. The maximum deviation is 122%, which occurred for extraction with pure ethanol at a low extraction rate.

Table 6. Correlation results and their error margins.

Experiment number	R_a^2	Y_{yield}	Y_{calc}	Dev. [%]
1	512.9	75.88	75.93	0.07
2	314.0	86.16	87.88	2.00
3	187.1	66.15	63.27	4.35
4	132.3	48.45	49.60	2.36
5	149.5	24.31	53.91	121.77
6	130.6	56.75	55.43	2.34
7	133.7	71.05	62.90	11.46
8	155.4	87.34	87.81	0.54
9	143.0	87.28	65.80	24.62
10	169.0	130.34	124.31	4.63
11	203.0	114.65	84.54	26.26
12	144.1	41.50	83.30	100.73

$$\text{Dev. [\%]} = \left| Y_{\text{yield}} - Y_{\text{calc}} \right| Y_{\text{yield}} \times 100$$

4. Conclusion

Mangiferin was successfully extracted from mango leaves using an environmentally friendly solvent system consisting of ethanol, water, and liquid CO_2 . In the ethanol–water binary system, the highest

extraction yield was achieved at an ethanol volume fraction of 25%, reflecting mangiferin's strong hydrogen-bonding affinity for the water-rich solvent. The addition of liquid CO₂ further enhanced extraction efficiency by improving mass transfer and solvent permeability. A thermodynamic model based on HSP was developed, and $\ln(Y)$ was correlated as a function of R_a and the volume fraction of CO₂, the entrainer. The extraction yield could be quantitatively expressed by the thermodynamic model based on HSP for solvents containing low to moderate amounts of ethanol with high extraction rates while accounting for the effect of CO₂ addition. This study demonstrates the importance of mango leaves as a sustainable source of mangiferin, provides a rational framework for designing green extraction processes for polar phytochemicals, and shows that a thermodynamic model based on HSP can quantitatively express the effect of CO₂ as a co-solvent on extraction yield.

Acknowledgement

This study was supported by Grants-in-Aid for Scientific Research (Nos. 23K04482 and 25K08371) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Declaration

The authors declare that they have no conflict of interest.

References

- 1) M. Kumar, V. Saurabh, M. Tomar, M. Hasan, S. Changan, S. Sasi, C. Maheshwari, U. Prajapati, S. Singh, R. K. Prajapat, S. Dhumal, S. Punia, R. Amarowicz, M. Mekhemar, *Antioxidants*, **10**, 299 (23 pages) (2021).
- 2) M. Işık, E. Dikici, S. Altın, C. Alp, K. K. Kirboğa, E. Köksal, Ş. Beydemir, *Food Sci. Nutr.*, **13**, e70263 (9 pages) (2025).
- 3) G. Lawrence, I. Marchaux, E. Pejcz, A. Wojciechowicz-Budzisz, R. Olędzki, A. Zając, O. Paroń, G. Aurore, J. Harasym, *Molecules*, **30**, 3381 (18 pages) (2025).
- 4) S. Laulloo, M. Bhowon, S. Soyfoo, L. Chua, *J. Chem.*, **2018**, 6869294, (9 pages) (2018).
- 5) J. Pan, X. Yi, S. Zhang, J. Cheng, Y. Wang, C. Liu, X. He, *Ind. Crops Prod.*, **111**, 400-406 (2018).
- 6) G. Sferrazzo, R. Palmeri, C. Restuccia, L. Parafati, L. Siracusa, M. Spampinato, G. Carota, A. Distefano, M. Di Rosa, B. Tomasello, A. Costantino, M. Gulisano, G. L. Volti, I. Barbagallo, *Antioxidants*, **11**, 1313 (15 pages) (2022).
- 7) T. Zou, H. Wu, H. Li, Q. Jia, G. Song, *J. Sep. Sci.*, **36**, 3457-3462 (2013).
- 8) P. Kaur, R. C. Gupta, A. Dey, T. Malik, D. K. Pandey, *Sci. Rep.*, **11**, 16346 (16 pages) (2021).
- 9) T. Arumugham, K. Rambabu, S. W. Hasan, P. L. Show, J. Rinklebe, F. Banat, *Chemosphere*, **271**, 129525 (19 pages) (2021).
- 10) K. Mishima, R. Kawakami, H. Yokota, T. Harada, T. Kato, H. Kawamura, K. Matsuyama, S. Mustofa, F. Hasanah, Y. D. I. Siregar, L. S. E. Putri, A. Salim, *Solvent Extr. Res. Dev., Jpn.*, **21**, 55-63 (2014).
- 11) R. Mitani, H. Tashiro, E. Arita, K. Ono, M. Haraguchi, S. Tokunaga, T. Sharmin, T. M. Aida, K. Mishima, *Sep. Sci. Technol.*, **56**, 290-300 (2021).

- 12) M. T. Fernández-Ponce, L. Casas, C. Mantell, M. Rodríguez, E. Martínez de la Ossa, *J. Supercrit. Fluids*, **72**, 168-175 (2012).
- 13) C. M. Hansen, *Hansen Solubility Parameters*, 2nd ed., CRC Press, Boca Raton, 1-519 (2007).
- 14) S. Abbott, *Curr. Opin. Colloid Interface Sci.*, **48**, 65-76 (2020).
- 15) A. del Pilar Sánchez-Camargo, M. Bueno, F. Parada-Alfonso, A. Cifuentes, E. Ibáñez, *TrAC, Trends Anal. Chem.*, **118**, 227-237 (2019).
- 16) I. Gupta, S. N. Adin, M. Aqil, M. Mujeeb, *Pharmacogn. Res.*, **15**, 145-154 (2023).
- 17) Z. Tofighi, M. Khoshayand, M. Mofasseri, M. P. Hamedani, M. T. Nasrabadi, A. M. Abhagi, A. Hadjiakhoondi, S. Goodarzi, Jundishapur, *J. Nat. Pharm. Prod.*, **20**, e151857 (16 pages) (2025).
- 18) T.-B. Zou, E.-Q. Xia, T.-P. He, M.-Y. Huang, Q. Jia, H.-W. Li, *Molecules*, **19**, 1411-1421 (2014).
- 19) H. Renon, J. M. Prausnitz, *AIChE J.*, **14**, 135-144 (1968).
- 20) D.-Y. Peng, D. B. Robinson, *Ind. Eng. Chem. Fundam.*, **15**, 59-64 (1976).
- 21) B. E. Poling, J. M. Prausnitz, J. P. O'Connell, *The Properties of Gases and Liquids*, 5th ed., McGraw-Hill, New York (2001).
- 22) M.-J. Huron, J. Vidal, *Fluid Phase Equilib.*, **3**, 255-271 (1979).
- 23) S. I. Sandler, *Chemical and Engineering Thermodynamics*, 3rd ed., Wiley, New York 1-587 (1999).
- 24) H. Inomata, A. Kondo, K. Arai, S. Saito, *J. Chem. Eng. Jpn.*, **23**, 199-207 (1990).