Solubilities in Supercritical Carbon Dioxide of (2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol (Farnesol) and (2*S*)-5,7-Dihydroxy-2-(4-hydroxyphenyl)chroman-4-one (Naringenin)

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We measured the solubility in supercritical carbon dioxide (CO_2) of farnesol [(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol] and naringenin [(2*S*)-5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one] using a static-analytic method (a high-pressure static equilibrium cell coupled to an HPLC). The molar fraction of farnesol in the saturated CO_2-rich phase increased between $y_2 = 0.13 \cdot 10^{-3}$ at 333 K and 11.4 MPa to $y_2 = 1.91 \cdot 10^{-3}$ at 333 K and 26.0 MPa for farnesol and from $y_2 = 0.49 \cdot 10^{-5}$ at 313 K and 10.3 MPa to $y_2 = 1.65 \cdot 10^{-5}$ at 333 K and 44.5 MPa for naringenin. The average error of our measurements was about 25 %. Farnesol had an end-temperature crossover point at approximately 17 MPa, whereas naringenin exhibited a monotonous increase in solubility with both temperature and pressure. The differences in solubility between farnesol, naringenin, and other sesquisterpenes or flavonoids reported in the literature were partially explained by differences in molecular weight and polarity between solutes. We correlated experimental data as a function of the system temperature and pressure and the density of the solvent using a literature model that also showed the autoconsistency of the data for CO_2 densities above 412 kg·m^{-3} for naringenin.

Introduction

There is worldwide interest in the development of functional foods (regular dietary nutrients that promote good health and prevent or alleviate chronic diseases) and nutraceuticals (extracts having same health benefits of functional foods that are instead consumed in prescribed doses using a medicinal format) from biological materials,[1] particularly from food processing byproducts such as those of citrus juice plants. Large supplies of residual peels, seeds, and pulp from citrus juice plants in industrialized countries have prompted the recovery, purification, and concentration of volatile oils, flavonoids, and other fractions that can be used as ingredients in nutraceuticals and functional foods.[2]

Extraction solvents for nutraceuticals include water, ethanol, and their mixtures for polar compounds and *n*-hexane for nonpolar compounds. However, the regulated upper limit of residual *n*-hexane in food extracts has decreased steadily to prevent toxic effects in humans.[3] The extraction with near- and supercritical carbon dioxide (CO_2), which we will refer to as supercritical CO_2 (SC-CO_2) extraction, is an attractive alternative to conventional low-pressure extraction with *n*-hexane because CO_2 is inert, nontoxic, nonflammable, and inexpensive, and it can be used as a nonpolar solvent at near environmental temperatures thus minimizing process-heat requirements and avoiding damage to thermolabile compounds.[4] The solvent power of SC-CO_2 (which is a strong function of the density of the CO_2 and to a lesser extent of the temperature) is high but variable due to the liquid-like density and high compressibility of the CO_2, particularly under near-critical conditions. This is responsible for the high selectivity and tunability of the SC-CO_2, which can extract increasingly heavier and/or more polar compounds when increasing the pressure.

Relevant low-molecular weight and/or nonpolar citrus components having desirable nutraceutical properties that may potentially be solubilized by SC-CO_2 include terpenoids and flavonoids. Terpenoids are compounds derived from isoprene [2-methyl-1,3-butadiene, a five-carbon (C-5) unsaturated hydrocarbon] and include monoterpene (C-10) hydrocarbons, sesquiterpene (C-15) hydrocarbons, triperpene (C-30) hydrocarbons, tetraterpene (C-40) hydrocarbons (or carotenes), and oxygen-containing compounds derived from them. Ductless glands in the flavedo (outer portion) of citrus peels contain volatile monoterpenes and sesquiterpenes (1 % to 2.5 % in the case of bitter orange)[5] that are responsible (mainly minoritary oxygenated monoterpenes) for the characteristic aroma of citrus fruits. A group of oxygen-containing triperpene derivatives, the limonoids, is responsible for the bitter flavor of some citrus fruits; based on literature data,[6,7] we estimated that the approximate content of limonoids (mostly limonin and nomilin) in peels of mature citrus fruits ranges from about 5 ppm (d.b.) in grapefruit to about 700 ppm (d.b.) in tangerine. Carotenoids (carotenes and oxygen-containing xanthophylls) are responsible for the yellowish to redish color of citrus fruits; the total carotenoid content in peels of Taiwanese citrus fruits ranges from 15 ppm (d.b.) in lemon (about 70 % β-carotene) to 110 ppm (d.b.) in orange (about 45 % β-carotene).[8] There is extensive literature on the bioactivity and potential as nutraceuticals of carotenoids[9−13] and citrus flavonoids.[2,6,14,15]

Besides terpenoids, there are several flavonoids in citrus fruits that can be extracted, purified, and concentrated using SC-CO_2

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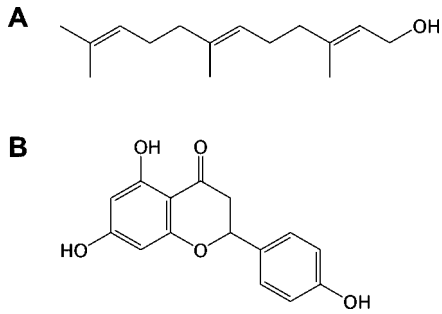

Figure 1. Chemical structure of (**A**) farnesol and (**B**) naringenin.

and deserve attention because of their potential as ingredients for nutraceuticals and functional foods. Peels of selected Taiwanese citrus fruits contain 3.5 % (d.b.) to 5 % (d.b.) flavonoids which are in turn classified, in decreasing order of importance, as flavanones (90 % to 96 % of all flavonoids), flavonols (3 % to 6.5 % of all flavonoids), or flavones (0.5 % to 3.5 % of all flavonoids).[8] Main flavanones are naringin in grapefruit (97 % of all flavononones) and hesperidin in lemon (85 %), orange (98 %), and tangerine (98 %), whereas quercetin content ranges from 20 % of all flavonols in orange to 40 % in tangerine (in which it is the most important flavonol).[8] Many of these flavonoids are found in plants as water-soluble glycosides to facilitate transport and storage in the tissue while avoiding deterioration by heat, ultraviolet radiation, and oxidation, but the water-insoluble and chemically unstable aglycones must be freed in situ by enzymatic hydrolysis of the bond with the sugar moieties to allow the biological activities of the flavonoids to the expressed.[16] The decrease in both molecular weight and polarity resulting from the hydrolysis of naringin or hesperidin increase the solubility in SC-CO_2 of resulting naringenin or hesperetin, respectively, thus facilitating their extraction from citrus processing byproducts. There is extensive literature on the antimicrobial, antioxidant, and anti-inflammatory properties of citrus flavonoids.[17,18]

Representative SC-CO_2-based separation processes used in the literature to impart value-added properties to citrus peels and seeds include batch extraction of solid substrates (to extract essential oils[19−22] and coumarins[23] from citrus peels and limonin from grapefruit seed[24]), continuous countercurrent extraction/purification of liquids (to extract phenolics and flavonoids in orange juice[25] and to deterpenate citrus essential oils[26−32]), and swing adsorption/desorption purification processes using silica gel as a complementary separating agent (to deterpenate and/or remove waxes, coumarins, and/or psoralens from citrus essential oils[32−35]). The optimization of these separation processes is easier when knowing the thermodynamic solubility in CO_2 of representative solutes in the substrate and/or their partition coefficients between CO_2 and an aqueous or lipidic liquid phase or a solid adsorbent as a function of system temperature and pressure, depending on the process.

In this work, we measured the solubilities in SC-CO_2 of farnesol and naringenin as a function of system temperature and pressure because of their content in residual peels from citrus juice plants and their bioactivities and potential as ingredients for nutraceuticals and functional foods. Farnesol [(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trien-1-ol; Figure 1A], an oxygenated sesquiterpene that constitutes about 10 % of the whole fraction, 1 % of all sesquiterpenes, and 0.02 % of all volatile oils in a lemon variety,[36] has antifungal[37,38] and anticancer[39−42] properties. Naringenin [(2*S*)-5,7-dihydroxy-2-(4-hydroxyphenyl)chroman-4-one; Figure 1B], the aglycone resulting from the enzymatic cleavage of the sugar (neohesperidose) moiety of naringin, the naturally occurring flavanone glycoside in citrus fruits,[43,44] has proven antimicrobial, antioxidant, and anti-inflammatory properties.[17,18]

Experimental Section

Materials. For phase equilibrium measurements, we used farnesol ($w = 0.96$, liquid) and naringenin ($w = \sim 0.95$, solid), both from Sigma-Aldrich (St. Louis, MO), as the solutes and food quality ($w = 0.9999$) CO_2 from AGA-Chile S.A. as the solvent. For preparation of mobile phases for HPLC analyses, on the other hand, we used methanol and acetonitrile from JT Baker (Phillipsburg, NJ) and locally deionized, doubly distilled, and microfiltered (filter openings of 2 μm diameter) water.

Solubility Measurements. We measured the solubility of farnesol and naringenin in SC-CO_2 at (313, 323, and 333) K and over a pressure range of (10 to 44) MPa using the experimental device and static-analytic methodology of de la Fuente et al.[45] We loaded samples of 10 g of farnesol or 0.5 g of naringenin in a 50 cm^3 equilibrium cell[46] together with CO_2. Following 12 h equilibration at the desired absolute temperature and pressure, we measured the concentration of the solute (component 2) in the saturated CO_2 (component 1) phase by online HPLC analysis of at least three 20 μL aliquots. For each measurement, we withdrew an aliquot from the equilibrium cell using a six-port, two-position high-pressure valve that coupled the cell with an HPLC apparatus,[45] observing variations in pressure of $\leq$ 0.2 MPa while sampling. We then separated the solutes in a reverse-phase C18 column (LiCroCART, Merck, Darmstadt, Germany) and estimated the solubility (y_2, mole fraction of the solute in the saturated CO_2-rich phase) from the chromatographic peak areas and those of standard methanolic solutions containing 200 ppm of farnesol or 500 ppm of naringenin.[45] The separation temperature, the flow rate, and composition of the mobile phase and the detection wavelength in the UV/vis apparatus farnesol were, respectively, as follows: 1.0 $cm^3 \cdot min^{-1}$ of a 85/15 (v/v) mixture of acetonitrile and water, 313 K, and 290 nm.[47] Corresponding values for naringenin were, respectively, 0.9 $cm^3 \cdot min^{-1}$ of a 52/48 (v/v) mixture of methanol and water, 328 K, and 250 nm.[43]

Data Correlation and Analysis. We correlated the experimental solubility data by best-fitting the values of parameters *A*, *B*, and *C* in the equation of Méndez-Santiago and Teja[48] (eq 1)

$$\ln(y_2 P) = A + \frac{B + C\rho_1}{T} \tag{1}$$

where *T* is the absolute temperature; *P*is the pressure; and ρ_1 is the density of the saturated CO_2-rich phase. We estimated model parameters *A*, *B*, and *C* by multivariate linear regression of experimental values of $\ln(y_2 P)$ vs T^{-1} and ρ_1/T using an Excel spreadsheet. To do so, we assumed ρ_1 was not affected by dissolution of the solute in the CO_2-rich phase, which is reasonable under low-loading (for low-solubility solutes) conditions, and estimated ρ_1 as a function of *T* and *P* by using NIST Standard Database v5.0 for pure CO_2.[49]

Equation 1 is used to test the autoconsistency of experimental solubility isotherms[45,46,48,50,51] because, when rearranged as eq 2, it predicts that values of the function $\Psi(T,P,y_2)$ collapse to a single, solute-dependent line, when plotted against ρ_1

$$\psi\{=T[\ln(y_2 P) - A]\} = B + C\rho_1 \tag{2}$$

Table 1. Solubility Isotherms for Farnesol in Supercritical CO_2 at (313, 323, and 333) K[a]

T/K = 313		T/K = 323		T/K = 333	
P	y_2	P	y_2	P	y_2
MPa	10^3 mol·mol^{-1}	MPa	10^3 mol·mol^{-1}	MPa	10^3 mol·mol^{-1}
9.70	0.83 ± 0.03	9.74	0.23 ± 0.08	11.4	0.13 ± 0.00
9.75	0.89 ± 0.03	9.74	0.19 ± 0.08	11.5	0.13 ± 0.00
9.75	0.83 ± 0.03	10.1	0.26 ± 0.05	11.5	0.13 ± 0.00
10.2	0.84 ± 0.03	10.1	0.22 ± 0.05	13.3	0.45 ± 0.03
10.2	0.89 ± 0.03	10.2	0.24 ± 0.02	13.3	0.43 ± 0.03
10.3	0.87 ± 0.06	10.2	0.21 ± 0.02	13.4	0.49 ± 0.03
12.0	0.90 ± 0.00	11.6	0.53 ± 0.05	15.3	0.92 ± 0.02
12.0	0.88 ± 0.01	11.7	0.48 ± 0.05	15.4	0.96 ± 0.02
12.4	0.90 ± 0.00	11.7	0.56 ± 0.01	15.4	0.95 ± 0.02
12.5	0.95 ± 0.00	14.5	1.04 ± 0.16	17.2	1.10 ± 0.03
12.6	0.97 ± 0.00	14.6	0.98 ± 0.12	17.3	1.16 ± 0.03
13.8	1.06 ± 0.00	14.7	1.09 ± 0.10	17.4	1.14 ± 0.03
14.1	1.05 ± 0.06	16.4	1.04 ± 0.02	19.2	1.44 ± 0.23
16.2	1.12 ± 0.05	16.5	1.01 ± 0.02	19.4	1.47 ± 0.23
16.5	1.17 ± 0.00	16.7	1.00 ± 0.02	19.4	1.49 ± 0.25
16.9	1.13 ± 0.04	20.3	1.33 ± 0.50	20.6	1.63 ± 0.19
17.1	1.19 ± 0.04	20.5	1.36 ± 0.43	20.7	1.69 ± 0.19
20.1	1.22 ± 0.00	20.8	1.34 ± 0.43	22.6	1.64 ± 0.11
20.3	1.22 ± 0.00			22.9	1.82 ± 0.14
				25.6	1.81 ± 0.43
				26.0	1.91 ± 0.45

[a] y_2 is the molar fraction of farnesol in a saturated CO_2 phase at a system temperature T and pressure P.

To discuss the differences in the solubility in SC-CO_2 between farnesol or naringenin and the solubilities of other sesquiterpenes or flavonoids reported in the literature, we estimated the corresponding solubility parameters (δ_2) at 298 K of the different solutes by using the group contribution method of Barton[52] and then corrected the values of δ_2 to (313 or 318) K using the equation of Galia et al.[53] This temperature correction depended on the critical temperature of the solutes, which we estimated using the method of Joback using group contribution values listed by Poling et al.[54] We estimated the solubility parameter of SC-CO_2 (δ_1) as a function of its density ρ_1 using the equation of Giddings et al.[55]

Results and Discussion

Solubilility of Farnesol in Supercritical Carbon Dioxide. Table 1 reports the solubility of farnesol in SC-CO_2 as a function of system temperature and pressure, which increased from $y_2 = 0.13 \cdot 10^{-3}$ at 333 K and 11.4 MPa to $y_2 = 1.91 \cdot 10^{-3}$ at 333 K and 26.0 MPa. The estimated relative error in these solubility measurements was 25 %, with uncertainties in the sampling system representing 80 % of the total error.[51]

Solubility isotherms (plots not shown) showed that the solubility of farnesol increased as the pressure increased because of the increase in density (and solvent power) of the SC-CO_2. We also identified an end-temperature crossover at about 17 MPa: below 17 MPa, the solubility of farnesol decreased as the temperature increased because of the decrease in density (and solvent power) of the SC-CO_2; above 17 MPa, the solubility increased with temperature because of the increase in vapor pressure (and volatility) of the farnesol; and at about 17 MPa, the solubility remained constant because the increase in vapor pressure and volatility of farnesol resulting from the increase in temperature compensated the decrease in density and solvent power of SC-CO_2.[4] Consequently, the increase in solubility with pressure was less pronounced at 313 K than 333 K (a 2- versus a 7.5-time increase when pressure increased from (10 to 20) MPa).

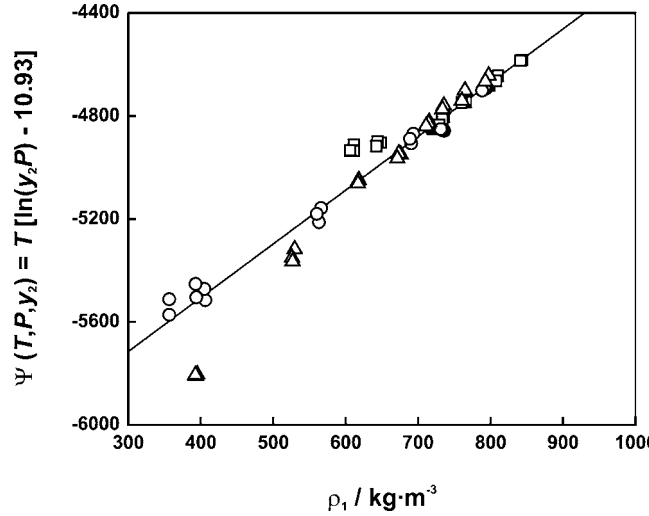

Figure 2. Solubility function $\Psi = T[\ln(y_2P) - 10.93]$ versus solvent density (ρ_1) showing the collapse of experimental isotherms for farnesol in supercritical CO_2 to a single best-fit line. □, 313 K; ○, 323 K; △, 333 K; line, corresponds to the best-fit eq 3.

When fitting eq 1 to the experimental data in Table 1 we obtained an explicit expression for y_2 (mol of farnesol per mol of SC-CO_2) as a function of T (K), P (MPa), and ρ_1 (kg·m^{-3}), eq 3

$$y_2 = \frac{1}{P}\exp\left(10.93 - \frac{6332 - 2.081\rho_1}{T}\right) \qquad (3)$$

Figure 2 presents the experimental values of $\Psi = T[\ln(y_2P) - 10.93]$, computed using the best-fit value of parameter A (10.93) informed in eq 3. Despite data scattering, it is apparent from Figure 2 that Ψ increases linearly with ρ_1, with the exception of a few experimental points using low-density ($\rho_1 \leq 395$ kg·m^{-3}) SC-CO_2 at 333 K, and that this increase is temperature-independent, as predicted by eq 2. The average absolute deviation (AAD) between the experimental solubilities in Table 1 and the corresponding values predicted by eq 3 was 47 %.

Farnesol is less soluble in SC-CO_2 than typical lower molecular weight citrus volatile oil components such as monoterpene hydrocarbons (e.g., limonene) and oxygenated monoterpenes (e.g., citral, linalool). Because the critical pressure at 313 K of the CO_2 + limonene binary system is about (8.3 to 8.5) MPa,[56,57] limonene (a low-molecular weight and low-polarity solute) is fully miscible with SC−CO_2 at 313 K and above (8 to 9) MPa. On the basis of experimental data of Budich and Brunner[58] on the CO_2 + orange peel oil multicomponent system [constituted of 98.25 % (w/w) monoterpene hydrocarbons and 1.75 % oxygenated monoterpenes, with limonene representing 96.7 % of all monoterpene hydrocarbons and linalool representing 28.8 % of all oxygenated monoterpenes], we estimated that the critical point of the mixture increased from about 10 MPa at 323 K, to about 12 MPa at 333 K, and to about 14 MPa at 343 K.

Table 2 compares the solubility in SC-CO_2 at 313 K and 15 MPa predicted by eq 3 for farnesol, with the corresponding solubilities of the sesquiterpene hydrocarbons humulene[35] and caryophyllene[59] and of the oxygenated sesquiterpenes patchoulol[60] and artemisinin.[61,62] Unlike many C-15 monoterpene compounds that are fully miscible with SC-CO_2 at 313 K and 15 MPa, the solubility of C-20 sesquiterpene compounds is

Table 2. Comparison of the Solubilities (y_2) of Farnesol (Predicted by Equation 3) and Sesquiterpene Hydrocarbons Humulene or Caryophyllene or Oxygenated Sesquiterpenes Patchoulol or Artemisinin, in Supercritical CO_2 at 313 K and 15 MPa[a]

compound	MW_2 / Da	δ_2 / $MPa^{0.5}$	y_2 / 10^3 mol·mol^{-1}	ref
humulene	204.4	17.06	3.21	Michielin et al.[35]
caryophyllene	204.4	18.19	3.01	Michielin et al.[35]
farnesol	222.4	19.79	1.10	This work
patchoulol	222.4	20.56	4.00	Hybertson[36]
artemisinin	282.3	23.80	1.27	Xing et al.[37]
			1.27	Coimbra et al.[40]

[a] The value of the solubility parameter of CO_2 under these conditions is $\delta_1 = 12.29$ $MPa^{0.5}$. MW_2 is the molecular weight of the solute and δ_2 its solubility parameter at 313 K.

Table 3. Solubility Isotherms for Naringenin in Supercritical CO_2 at (313, 323, and 333) K[a]

T/K = 313		T/K = 323		T/K = 333	
P / MPa	y_2 / 10^5 mol·mol^{-1}	P / MPa	y_2 / 10^5 mol·mol^{-1}	P / MPa	y_2 / 10^5 mol·mol^{-1}
10.3	0.49 ± 0.08	10.2	0.59 ± 0.57	10.7	0.68 ± 0.20
10.4	0.55 ± 0.08	15.3	0.68 ± 0.11	15.4	0.79 ± 0.05
14.7	0.59 ± 0.34	15.4	0.74 ± 0.10	20.4	0.93 ± 0.18
15.0	0.66 ± 0.39	15.4	0.71 ± 0.11	20.4	0.88 ± 0.20
19.9	0.73 ± 0.36	19.6	0.82 ± 0.02	20.7	0.94 ± 0.26
20.5	0.74 ± 0.23	20.6	0.85 ± 0.37	24.9	1.13 ± 0.21
29.5	0.84 ± 0.54	20.9	0.83 ± 0.37	25.5	1.06 ± 0.21
29.9	0.95 ± 1.20	24.8	0.87 ± 0.01	30.1	1.24 ± 0.34
30.3	0.84 ± 0.33	25.0	0.87 ± 0.01	30.3	1.08 ± 0.32
33.7	0.93 ± 0.02	25.2	0.89 ± 0.08	34.6	1.24 ± 0.39
33.9	0.95 ± 0.02	25.3	0.92 ± 0.08	34.9	1.15 ± 0.22
34.2	0.95 ± 0.01	25.5	0.88 ± 0.11	35.3	1.17 ± 0.31
34.6	0.96 ± 0.19	25.7	0.95 ± 0.04	35.6	1.25 ± 0.48
35.0	1.04 ± 0.12	25.8	0.88 ± 0.05	40.8	1.49 ± 0.11
35.0	0.96 ± 0.12	29.0	0.98 ± 0.07	40.8	1.34 ± 0.11
35.1	1.00 ± 0.15	29.4	0.96 ± 0.12	44.5	1.65 ± 0.33
36.4	0.93 ± 0.06	30.1	1.00 ± 0.24		
36.9	1.02 ± 0.06	34.4	1.04 ± 0.10		
43.8	1.14 ± 0.06	36.2	1.13 ± 0.09		
44.3	1.05 ± 0.05	41.0	1.27 ± 0.38		
		43.2	1.30 ± 0.42		
		43.7	1.38 ± 0.42		
		44.3	1.24 ± 0.29		

[a] y_2 is the molar fraction of naringenin in a saturated CO_2 phase at a system temperature T and pressure P.

limited to (1 to 4)·10^{-3} under those conditions. We expected the solubility to decrease as a result of an increase in the molecular weight and polarity of solute, which is partially reflected by an increase in the computed value of the solubility parameter, and this was observed when comparing the solubility of farnesol with the extrapolated values for humulene and caryophyllene from data of Michielen et al.[59] The solubility of farnesol we measured was smaller than the solubility of patchoulol (same molecular weight, approximately same solubility parameter) reported by Hybertson[60] and similar to the solubility of artemisinin (heavier, more polar) interpolated from data of either Xing et al.[61] or Coimbra et al.,[62] which was unexpected.

Solubilility of Naringenin in Supercritical Carbon Dioxide. Table 3 reports the solubility of naringenin in SC-CO_2 as a function of system temperature and pressure. The molar fraction of naringenin in the CO_2-rich phase increased from $y_2 = 0.49 \cdot 10^{-5}$ at 313 K and 10.3 MPa to $y_2 = 1.65 \cdot 10^{-5}$ at 333 K and 44.5 MPa. In this case, and similar to the measurements with farnesol, the estimated relative error was 24 %, and uncertainties associated with sampling accounted for 83 % of the total error.[51]

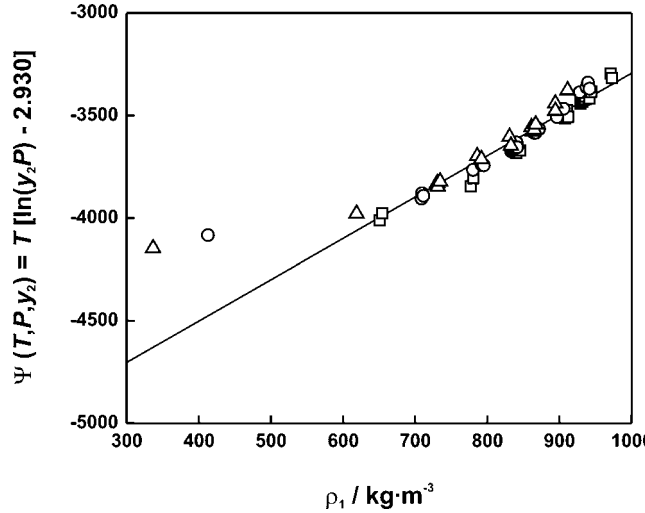

Figure 3. Solubility function $\Psi = T[\ln(y_2P) - 2.930]$ versus solvent density (ρ_1) showing the collapse of experimental isotherms for naringenin in supercritical CO_2 to a single best-fit line. □, 313 K; ○, 323 K; △, 333 K; line, corresponds to the best-fit eq 4.

Table 4. Comparison of the Solubilities (y_2) of Naringenin (Predicted by Equation 4) and Several Flavonoids Including Flavone, 3-Hydroxyflavone, 7,8-Dihydroxyflavone, and Quercetin in Supercritical CO_2 at 318 K and 25.3 MPa[a]

flavonoid	MW_2 / Da	δ_2 / $MPa^{0.5}$	y_2 / mol·mol^{-1}	ref
flavone	222.2	24.47	$5.61 \cdot 10^{-4}$	Uchiyama et al.[39]
3-hydroxyflavone	238.2	28.59	$5.56 \cdot 10^{-5}$	Uchiyama et al.[39]
7,8-dihydroxyflavone	254.2	32.82	$3.88 \cdot 10^{-5}$	Matsuyamaet al.[40]
naringenin	272.3	35.62	$9.66 \cdot 10^{-6}$	this work
quercetin	302.2	45.83	$2.20 \cdot 10^{-5}$	Matsuyama et al.[40]

[a] The value of the solubility parameter of CO_2 under these conditions is $\delta_1 = 13.54$ $MPa^{0.5}$. MW_2 is the molecular weight of the solute and δ_2 its solubility parameter at 318 K.

Unlike farnesol, naringenin increased its solubility in SC-CO_2 with both system temperature and pressure under experimentally tested conditions, which suggests the increase in vapor pressure of the solute with temperature weighed more on changes in solubility than the decrease in density of the CO_2 within our experimental region. The increase in solubility with pressure was less pronounced at 313 K than 333 K (a 2- versus a 7-time increase when pressure increased from (10 to 20) MPa).

When fitting eq 1 to the experimental data in Table 3, we obtained eq 4 for y_2 (mol of naringenin per mol of SC-CO_2) as a function of T (K), P (MPa), and ρ_1 (kg·m^{-3})

$$y_2 = \frac{1}{P}\exp\left(2.930 - \frac{5308 - 2.013\rho_1}{T}\right) \text{(AAD = 37 \%)} \quad (4)$$

Figure 3 presents the plot of experimental values of $\Psi = T[\ln(y_2P) - 2.930]$ as a function of ρ_1 we used to test the autoconsistency of solubility isotherms for naringenin. The same as for farnesol, it is apparent that Ψ increases linearly with ρ_1 and that this increase does not depend on temperature, as predicted by eq 2, with the exception of a few data points obtained using low-density ($\rho_1 \leq 412$ kg·m^{-3}) SC-CO_2.

Table 4 compares the predicted solubility of naringenin in SC-CO_2 at 318 K and 25.3 MPa (eq 4), with corresponding solubilities of several flavonoids including flavone,[63] 3-hydroxyflavone,[63] 7,8-dihydroxyflavone,[64] and quercetin.[64] Table

4 shows a decrease in solubility (by a factor of about 60) between flavone and naringenin as a result of the increase in molecular weight and number of polar hydroxyl substituents (zero for flavones, one for 3-hydroxyflavone, two for 7,8-dihydroxyflavone, three for naringenin, and five for quercetin), which in our particular case is associated with an increase in the solubility parameter of these solutes. The solubility of quercetin in SC-CO_2 at 318 K and 25.3 MPa reported by Matsuyama et al.[64] that is shown in Table 4 is probably erroneous because Chafer et al.[65] observed very low solubilities [($<10^{-6}$ to 10^{-7}) mol·mol^{-1}] of quercetin in SC-CO_2 even at extreme conditions of 373 K and 40 MPa where the solvent power of SC-CO_2 is large, and the chromatographic peaks of quercetin were below the detection threshold of our HPLC system when we attempted measuring its solubility in SC-CO_2 even when using the top limit conditions of 333 K and 45 MPa of our experimental device. Thus, we believe the solubility of quercetin is possibly smaller instead of about the same as the solubility of naringenin in SC-CO_2 estimated using eq 4 under equivalent conditions. Differences between experimental methodologies applied to assess phase equilibrium partially account for discrepancies between experimental solubilities discussed in the literature[66,67] and may explain some of the inconsistencies noted in Table 2 and Table 4. Also, there are limitations in using solubility parameters as predictors of solute solubility in SC-CO_2, as exemplified by the differences in solubilities in ethanol-modified CO_2 at 313 K and 9 MPa between epicatechin and catechin, which differ from each other only on their spatial configuration (both have five polar hydroxyl substituents, MW = 290.3 Da, and $\delta_{318\ K} = 41.43$ MPa$^{0.5}$). Indeed solubilities of epicatechin reported by Cháfer et al.[68] are larger than corresponding solubilities of catechin reported by Berna et al.,[69] with differences ranging from 1.7 times as large when using 5 % ethanol as modifier to 13 times as large when using 25 % ethanol as modifier.

Conclusions

In this work, we measured the solubility of farnesol (a minority high-molecular weight and polar compound from the oxygenated sesquiterpene fraction of citrus essential oils) and naringin in SC-CO_2 at (313 to 333) K and (10 to 44) MPa. The solubility of farnesol in SC-CO_2 ranged from $y_2 = 0.13 \cdot 10^{-3}$ at 333 K and 11.4 MPa (the lowest tested pressure was 9.70 MPa at 313 K) to $y_2 = 1.91 \cdot 10^{-3}$ at 333 K and 26.0 MPa (the highest tested pressure) and exhibited an end-temperature crossover at about 17 MPa. On the other hand, the solubility of naringenin in SC-CO_2 was about 2 orders of magnitude smaller than the solubility of farnesol under equivalent conditions and ranged from $y_2 = 0.49 \cdot 10^{-5}$ at 313 K and 10.3 MPa (the lowest tested pressure was 10.2 MPa at 323 K) to $y_2 = 1.65 \cdot 10^{-5}$ at 333 K and 44.5 MPa (the highest tested pressure) and increased with both system temperature and pressure in the whole experimental region. These differences in solubility between farnesol and naringenin were explained by differences in molecular weight and polarity between the solutes, and these factors also explained to a certain extent the differences between the solubility in SC-CO_2 of farnesol we measured and those of other sesquiterpenes in the literature (which ranged from about $1 \cdot 10^{-3}$ to $4 \cdot 10^{-3}$ at 313 K and 15 MPa), as well as the differences between the solubility in SC-CO_2 of naringenin we measured and those of other flavonoids in the literature (which ranged from about $1 \cdot 10^{-5}$ to $60 \cdot 10^{-5}$ at 318 K and 25.3 MPa). We found that solubility data for both farnesol and naringenin were autoconsistent when using the test of Méndez-Santiago and Teja[48] for SC-CO_2 densities above 412 kg·m^{-3} for naringenin.

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