

# Vapour-Liquid Equilibrium (VLE) Modeling for Mixture of Carbon Dioxide / Ethanol / Water / Flavonoids

Teo Jia Le<sup>1</sup>, Masturah Markom<sup>1,\*</sup>, Muhammad Zulhaziman Mat Salleh<sup>1</sup>

Department of Chemical and Process Engineering, Faculty of Engineering & Built Environment, Universiti Kebangsaan Malaysia, 43600 Bangi, Selangor, Malaysia.

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**Abstract:** Supercritical fluid extraction (SFE) technology is an alternative for natural product extraction such as flavonoid. Supercritical carbon dioxide (scCO<sub>2</sub>) has been promoted in flavonoid extraction with the aid of co-solvents ethanol and water. This study will show the prediction data of flavonoid solubility in CO<sub>2</sub>/ethanol/water mixtures with the application of thermodynamic modelling using the Peng-Robinson equation of state (PR EOS). Vapor-liquid equilibria (VLE) of carbon dioxide (CO<sub>2</sub>)/ethanol/water ternary systems of predicted data shows Average Absolute Relative Deviations (AARD) of 5.1% and CO<sub>2</sub>/ethanol/water/flavonoid (flavone, 6-methoxyflavone and 7-hydroxyflavone) quaternary systems is discussed. Solubility study of flavonoid in scCO<sub>2</sub> with and without the presence of co-solvent is compared and predicted data shows AARD of 3.5%.

**Keywords:** *Flavonoid, Supercritical carbon dioxide, solubility, Peng-Robinson equation of state*

## 1. Introduction

Flavonoids are compounds that is commonly found in natural products such as corn and wheat, fruit, vegetables and beverages. This compound is widely applicable in various biomedical, pharmaceutical and industrial usage. Flavonoids were shown to have the potential of cardiovascular diseases, anti-allergy, antimicrobial and cancer-free activities aside from the prevention of inflammatory [1, 2]. Natural products are proven to contain health benefits to consumers through various research in recent years that gained prominence of public. These natural products such as phenolic compounds can be found in plant extracts. These phenolic compounds namely polyphenols are secondary metabolites of plant extracts. They can be classified into phenolic acids, tannins, simple phenols and flavonoids [3]. Phenolic acids contains

physical structure of a benzene ring linking to a carboxylic acid group one or multiple hydroxyls and/or methoxyl groups. The structure of these acids contributes in various health welfare and antioxidant properties, while enhancing condition of human body [4].

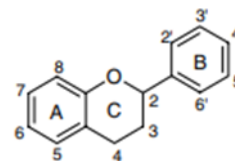


FIGURE 1. Basic Structure of flavonoids [5]

Extraction method, formulation method and crystallisation method are common processes applied in industrial scale flavonoids production in nutraceutical, food or pharmaceutical. The most recent and environmentally

**Corresponding Author:** Masturah Markom, Department of Chemical and Process Engineering, Universiti Kebangsaan Malaysia.

friendly extraction method is the supercritical carbon dioxide extraction (scCO<sub>2</sub>). The extraction efficiency from plant material is often limited by the solubility of the targeted compound in scCO<sub>2</sub>. However, solubility data is vital for process design optimization. Various literature data on the solubility measurement via scCO<sub>2</sub> has been published, but is still lacking in supporting the process design. This is due to the huge time consumption, high cost especially in preparation phase, and technical issue due to low expertise in handling and analysing the equipment [6]. To overcome the limitation and leverage the availability of the current scCO<sub>2</sub> data, application of the thermodynamic models of vapour-liquid equilibrium is used for solubility prediction through the importance of the thermophysical properties (critical temperature and pressure) and fugacity coefficient.

In this study Peng-Robinson equation of state (PR EOS) correlation was used for prediction of solubility data of scCO<sub>2</sub> extraction of flavonoids. PR EOS is commonly used for prediction of high pressure VLE data as compared to other modelling equations. The PR EOS is widely used for solubility modelling in supercritical fluids. This equation has been applied to predict the phase behavior of solutes with a wide range of volatility. Few assumptions are adopted to apply PR EOS as a prediction model for SCFs [7]. In this study, flavonoids assumed to remain as pure solid in solid phase; constant molar volume of the solute within tested range of pressure; and vaporised pure flavonoids behaves as an ideal gas [8]. This study aims to develop a prediction data of flavonoids solubility.

## 2. Methodology

### Flavonoids solubility and VLE database

Experimental data of supercritical carbon dioxide extraction of flavonoids were obtained from the literatures [9-12] and were used for prediction using PR EOS.

### PR-EOS thermodynamic modelling

For correlation of solubility data in supercritical fluids, the PR EOS [17] is commonly applied to determine the fugacity coefficient of the solute in the supercritical phase:

$$P = \frac{RT}{V_{mix} - b_{mix}} - \frac{\alpha_{mix}}{V_{mix}(V_{mix} + b_{mix}) + (b_{mix}(V_{mix} - b_{mix}))} \dots(1)$$

For mixtures of substances having large molecular size differences, the equation of state a and b are determined from the phase composition with the following relationships:

$$\alpha_{mix} = \sum_i \sum_j \alpha_{ij} y_i y_j \dots(2)$$

$$b_{mix} = \sum_i \sum_j b_{ij} y_i y_j \dots(3)$$

Where  $a_{ij}$  and  $b_{ij}$  are given by:

$$\alpha_{ij} = \sqrt{\alpha_i \alpha_j} (1 - k_{ij}) \dots(4)$$

$$b_{ij} = \frac{b_1 + b_2}{2} (1 - l_{ij}) \dots(5)$$

In Eqs. (4)–(5),  $k_{ij}$  and  $l_{ij}$  are adjustable parameters with  $k_{ji} = k_{ij}$  and  $l_{ji} = l_{ij}$  and  $k_{ii} = k_{jj} = 0$  and  $l_{ii} = l_{jj} = 0$ . Data regression for parameter  $k_{ij}$  has been made to ensure the best fitting parameter to be used for the data prediction. In the cubic equation of state model, sublimation pressure ( $P^{sub}$ ), solid molar volume ( $V$ ), critical temperature ( $T_c$ ), critical pressure ( $P_c$ ), acentric factor ( $\omega$ ) and mixture  $k_{12}$  and  $l_{12}$  values need to be estimated. The estimated parameters for the cubic equation of state model are shown in Table 1.

TABLE 1. Physical properties of CO<sub>2</sub>, ethanol, water and flavonoids [11].

Component	M/g.mol <sup>-1</sup>	Pc (bar)	Tc(K)	Acentric factor, $\omega$
CO <sub>2</sub>	44.01	73.76	304.2	0.225
EtOH	46.07	63.83	516.2	0.635
H <sub>2</sub> O	18.02	220.48	647.3	0.344
flavone	222.24	32.8	879.9	0.723
6-methoxyflavone	252.26	35.4	1062.5	0.914
7-hydroxyflavone	238.24	37.8	1074.2	0.952

### Solubility data prediction

Flavonoid solubility ( $y_{FA}$ ) is obtained by applying Eq. (1) on all solvents, which represents the impartiality of solute fugacity in both solid and liquid phase (light phase). Eq. (1) requires the fulfillment of following hypothesis: flavonoids assumed to remain as pure solid in solid phase; constant molar volume of the solute within tested range of pressure; and vaporised pure flavonoids behaves as an ideal gas.

$$y_{FA} = \frac{P_{sat}^{FA} \exp\left(\frac{V_{FA}(P - P_{sat}^{FA})}{RT}\right)}{\phi_{FA}^{lightphase} P} \dots(6)$$

$P_{FA}^{sat}$  is the saturation pressure at various temperature of flavonoids obtained in literature [13],  $V_{FA}$  is the molar volume of flavonoids and  $\phi_{FA}^{lightphase}$  is the fugacity coefficient of light flavonoids phase that can be obtained from the PR EOS.

### Average absolute relative deviations (AARD%)

After generation of predicted solubility data, the experimented values were compared with the predicted values by evaluation of relative deviation of the absolute average (AARD) as shown in Eq. (7). AARD will determine the data accuracy of predicted results. In this case, minimum AARD shall be obtained. The AARD is reduced after regression of binary interaction parameter  $k_{ij}$  with the “Goal Seek” function in Microsoft Excel.

$$AARD(\%) = \frac{1}{N} \sum_{i=1}^N \left( \frac{y_{exp,i} - y_{pred,i}}{y_{exp,i}} \times 100 \right) \dots(7)$$

The values obtained if its proven have less variance or could be said as accurate, the predicted data will be used to build phase diagram comprising CO<sub>2</sub>, ethanol, water and flavonoids.

**VLE in CO<sub>2</sub>(1) – ethanol(2) -water(3) ternary systems**

After the prediction data is calculated from the vapour-liquid equilibrium modelling using PR EOS, CO<sub>2</sub>–ethanol–water ternary systems is constructed and discussed. The construction of CO<sub>2</sub>–ethanol–water ternary system is used to compare the accuracy of data and solubility of three flavonoid which are flavones, 6-methoxyflavone and 7-hydroxyflavone. The solubility data of flavones, 6-methoxyflavone and 7-hydroxyflavone are also compared with difference in pressure to observe the effect of pressure on the solubility of the flavonoids. Effect of co-solvent ethanol and water on flavonoid is discussed in the following section.

**Comparison of flavonoid solubility data prediction**

Solubility data is predicted with PR EOS in equation (6). Solubility of flavonoids without co-solvent, with co-solvent ethanol and with co-solvent ethanol and water were plotted in graph and discussed further at various temperature and pressure. The AARD is identified with using the equation (7).

**4. Results and discussion**

**Predicted VLE data for CO<sub>2</sub>(1) – ethanol(2) -water(3)**

Experimental data obtained from literature was used for data prediction of CO<sub>2</sub>(1)–ethanol(2)–water(3) ternary system at 313.2K and 10MPa using PR EOS in Microsoft Excel. Data comparison of experimental and predicted mole fraction of CO<sub>2</sub>(1), ethanol(2), water(3) is shown in Table 2. The AARD% for vapour mole fraction, y of CO<sub>2</sub>(1), ethanol(2), water(3) are 7.21%, 0.43% and 7.64%. The average AARD% of predicted VLE is 5.1% with k<sub>ij</sub> regression. Low percentage of AARD indicates that this vapour-liquid equilibrium modelling is feasible to be applied and proves that PR EOS is favourable for supercritical fluid calculations. Binary interaction parameter k<sub>ij</sub> has been calculated and regressed with the minimum AARD which is k<sub>12</sub> = 0.402, k<sub>13</sub> = 0 dan k<sub>23</sub> = 0.299. k<sub>ij</sub> after regression is compared with Sato et al. (2019) [9] and [10]. ij in this study showed slightly lower AARD which is 5.1% compared to Sato et al. (2019) (5.88%) [9] and Durling et al. (2007) (6.99%) [10].

TABLE 2. Data comparison of experimental and predicted vapour mole fraction, y of CO<sub>2</sub>(1), ethanol(2) and water(3) at 313.2 K and 10 MPa

y-exp			y-pred			AARD (%)		
Y <sub>1</sub>	Y <sub>2</sub>	Y <sub>3</sub>	Y <sub>1</sub>	Y <sub>2</sub>	Y <sub>3</sub>	Y <sub>1</sub>	Y <sub>2</sub>	Y <sub>3</sub>
0.683	0.253	0.064	0.699	0.066	0.235	1.650	0.150	1.800
0.844	0.135	0.021	0.857	0.029	0.114	1.270	0.760	2.030
0.894	0.091	0.015	0.884	0.014	0.102	0.980	0.150	1.130
0.922	0.063	0.015	0.889	0.008	0.103	3.380	0.680	4.060
0.925	0.061	0.015	0.873	0.007	0.121	5.190	0.820	6.000
0.938	0.053	0.010	0.864	0.005	0.130	7.360	0.410	7.760
0.945	0.045	0.010	0.839	0.005	0.156	10.680	0.450	11.120
0.942	0.048	0.010	0.794	0.006	0.200	14.720	0.490	15.210
0.961	0.031	0.008	0.824	0.005	0.171	13.730	0.270	14.000
0.969	0.024	0.007	0.837	0.005	0.158	13.200	0.150	13.350
Average AARD (%)						7.21	0.43	7.64
Overall AARD (%)						5.1		

TABLE 3. Physical and thermophilic properties of CO<sub>2</sub>, ethanol, water and flavonoids. [9]

Sumber	k <sub>12</sub>	k <sub>13</sub>	k <sub>23</sub>	(AARD)%
This work	0.402	0	0.299	5.1
Sato et al. (2019)	0.423	0.0598	0.103	5.88
Durling et al. (2007)	0.0967	0.263	0.0257	6.99

**CO<sub>2</sub> (1) –ethanol (2) – water (3) ternary phase diagram**

Ternary phase diagram for CO<sub>2</sub> (1) – ethanol (2) – water (3) with the predicted and experiment data of vapour–liquid equilibrium at 313.2K and 10MPa is constructed using Microsoft Excel. Figure 2 shows that PR EOS can be applied in data prediction of supercritical CO<sub>2</sub> extraction method with low AARD of 5.1%. It is expected that the selection of mixing rules will affect the predicted result. In this study, we use conventional mixing rule to incorporate in PR EOS. The consistent curve along compared with exprimental data signifies the PR EOS to be applicable in supercritical conditions.

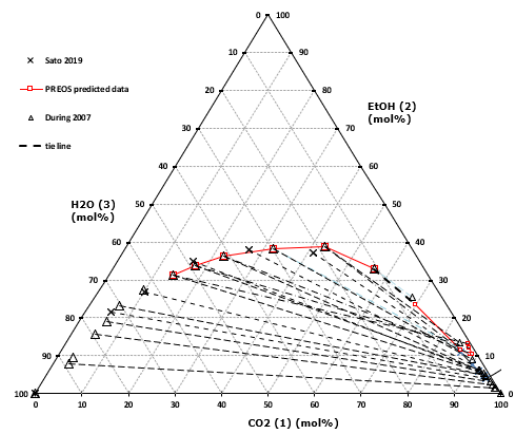


FIGURE 2 Ternary phase diagram of CO<sub>2</sub>(1) – ethanol(2) – water(3) at 313.2K and 10MPa. Symbol (x) and (Δ) indicates the data obtained from

Durling et al. (2007) and Sato et al. (2019), respectively. Predicted data that have been calculated as shown in Table 15 are plotted with the symbol of (□). Dotted lines ( - - ) represents the tie line of VLE data

**Solubility data prediction of flavonoid**

Table 4 shows the solubility data prediction of flavone, 6-methoxyflavone and 7-hydroxyflavone without co-solvent in temperature ranging from 313.2K to 333.2K and pressure ranging from 10 MPa to 22 MPa. The percentage difference is shown in Table 16. Predicted data shows the average AARD ranging from 0.0002% to 3.5044% with different temperature. This indicates that the predicted data is similar to experimental data.

TABLE 4.(a) Solubility data of flavone, 6-methoxyflavone and 7-hydroxyflavone without co-solvent

		flavone			
T (K)	P(MPa)	y <sub>2</sub> (10 <sup>4</sup> ) (EXP)	y <sub>2</sub> (10 <sup>4</sup> ) (PR EOS)	AARD (%)	Average AARD (%)
313.2	10	8.16	8.16	1.16 x 10 <sup>7</sup>	0.0002
313.2	14	21.4	21.4	1.21 x 10 <sup>7</sup>	
313.2	18	32.8	32.8	7.06 x 10 <sup>6</sup>	
313.2	22	42.7	42.7	8.4 x 10 <sup>6</sup>	

		6-methoxyflavone			
T (K)	P(MPa)	y <sub>2</sub> (10 <sup>8</sup> ) (EXP)	y <sub>2</sub> (10 <sup>8</sup> ) (PR EOS)	AARD (%)	Average AARD (%)
313.2	10	33.2	25.2	0.241	1.2382
313.2	15	119	119.122	0.103	
313.2	20	178	172	3.37	
323.2	10	8.9	8.9	1.81 x 10 <sup>3</sup>	3.5044
323.2	14	102	94	7.84	
323.2	18	179	173	3.35	
323.2	22	223	229.29	2.82	
333.2	10	8.65	8.65	3.52 x 10 <sup>4</sup>	0.9120
333.2	14	67	67	3.03 x 10 <sup>5</sup>	
333.2	18	193	193	8.24 x 10 <sup>6</sup>	
333.2	22	329	317	3.65	

		7-hydroxyflavone			
T (K)	P(MPa)	y <sub>2</sub> (10 <sup>9</sup> ) (EXP)	y <sub>2</sub> (10 <sup>9</sup> ) (PREOS)	AARD (%)	Average AARD (%)
313.2	18	18.8	18.8	2.05 x 10 <sup>3</sup>	0.0020
323.2	10	2.49	2.49	1.42 x 10 <sup>2</sup>	0.0066
323.2	14	16.1	16.1	5.62 x 10 <sup>3</sup>	
323.2	18	24.3	24.3	1.91 x 10 <sup>5</sup>	
333.2	14.1	17.9	17.9	1.81 x 10 <sup>5</sup>	0.0005
333.2	18	32.6	32.6	1.26 x 10 <sup>3</sup>	
333.2	22	39.1	39.1	1.59 x 10 <sup>4</sup>	

TABLE 4(b) Solubility data of flavone, 6-methoxyflavone and 7-hydroxyflavone with co-solvent ethanol

		flavone			
T (K)	P(MPa)	y <sub>3</sub> (10 <sup>3</sup> ) (EXP)	y <sub>3</sub> (10 <sup>3</sup> ) (PR EOS)	AARD (%)	Average AARD (%)
313.2	8	6.26	6.58	0.0323	0.0440
313.2	10	5.5	6.06	0.0556	

		6-methoxyflavone			
T (K)	P(MPa)	y <sub>3</sub> (10 <sup>3</sup> ) (EXP)	y <sub>3</sub> (10 <sup>3</sup> ) (PR EOS)	AARD (%)	Average AARD (%)
313.2	8	2.12	2.62	0.0496	0.0504
313.2	10	2.87	3.38	0.0512	

		7-hydroxyflavone			
T (K)	P(MPa)	y <sub>3</sub> (10 <sup>5</sup> ) (EXP)	y <sub>3</sub> (10 <sup>5</sup> ) (PREOS)	AARD (%)	Average AARD (%)
333.2	10	2.24	2.81	0.0006	0.0004
333.2	12	1.51	1.31	0.0002	

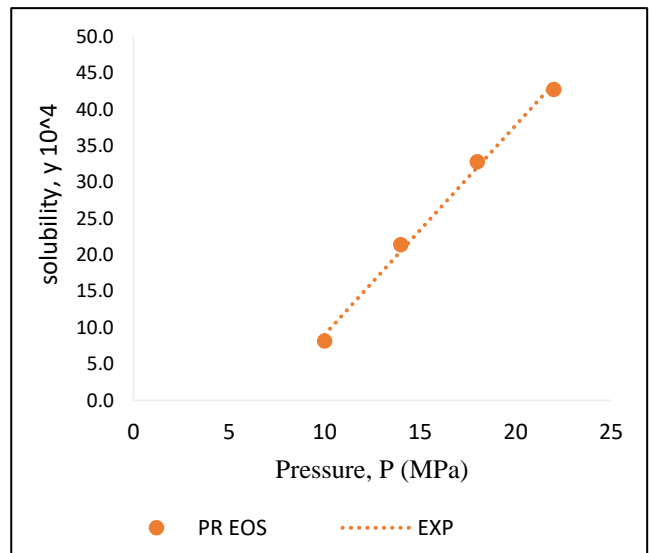
TABLE 4(c). Solubility data of flavone, 6-methoxyflavone and 7-hydroxyflavone with co-solvent ethanol and water

		flavone			
T (K)	P(MPa)	y <sub>4</sub> (EXP)	y <sub>4</sub> (PR EOS)	AARD (%)	Average AARD (%)
313.2	15	0.0245	0.0238	0.0654	0.05
313.2	20	0.0298	0.0294	0.0344	

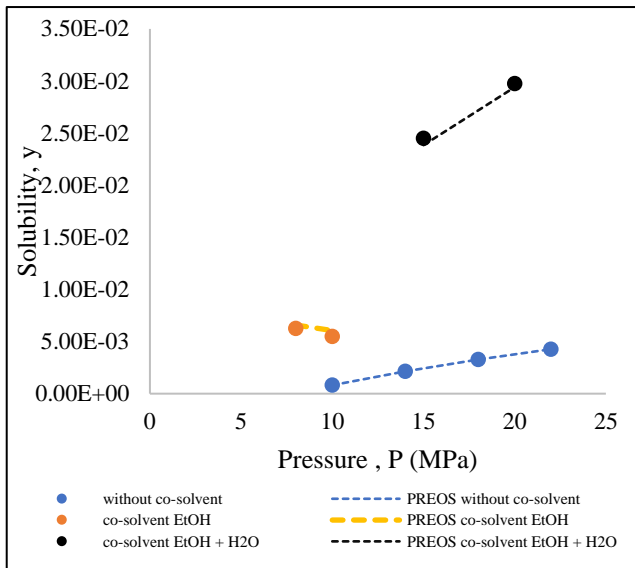
		6-methoxyflavone			
T (K)	P(MPa)	y <sub>4</sub> (EXP)	y <sub>4</sub> (PR EOS)	AARD (%)	Average AARD (%)
313.2	15	0.0218	0.0215	0.0271	0.08
313.2	20	0.03	0.0313	0.0132	

		7-hydroxyflavone			
T (K)	P(MPa)	y <sub>4</sub> (10 <sup>5</sup> ) (EXP)	y <sub>4</sub> (10 <sup>5</sup> ) (PR EOS)	AARD (%)	Average AARD (%)
313.2	15	7.75	7.46	0.003	0.0008
333.2	20	0.243	0.255	0.0013	

The difference of experimental and predicted data of flavonoid solubility with and without presence of co-solvent is shown on the first part (a) of Figure 3,4 and 5. In the second part, the solubility data is then compared with experimental data and predicted data with the presence of co-solvent ethanol and water as shown.



(a)

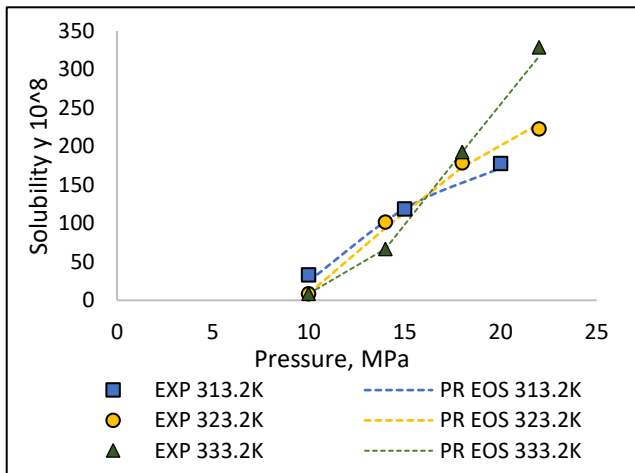


(b)

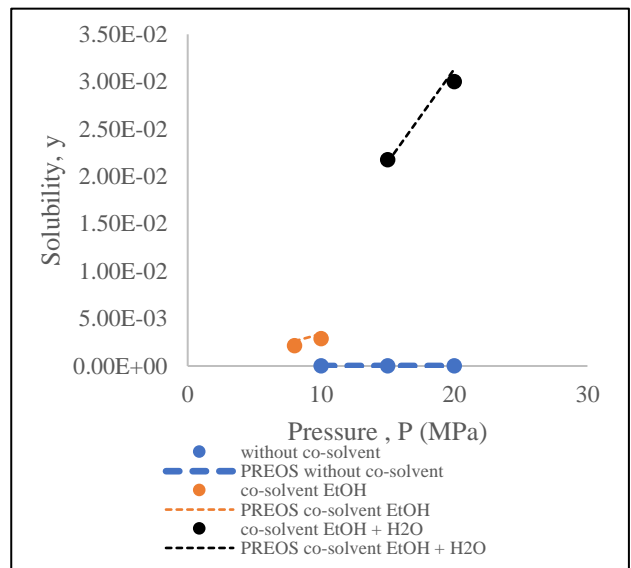
FIGURE 3 Solubility of flavone in 313.2K without co-solvent (a) and comparison of experimental data and predicted data of flavone solubility at 313.2K with co-solvent (b)

Figure 3(a) shows the comparison of predicted data with application of PR EOS and experimental data of flavone solubility in 313.2K. The figure indicates that the flavone solubility increases when pressure increases. Solubility of flavone shows the highest at 22MPa. There is a significant difference of solubility with the presence of co-solvent and without co-solvent. Figure 3(b) shows that co-solvent helps to improve the efficiency of supercritical fluid extraction by enhancing the solubility of flavone by increasing the polarity of flavonoid. It can be expected that the presence of co-solvent increased the polarity of the flavonoid and improved the extraction yield.

Figure 4(a) shows the comparison of predicted data with application of Peng-Robinson equation of state and experimental data of 6-methoxyflavone solubility in 313.2K, 323.2K and 333.2K [9].



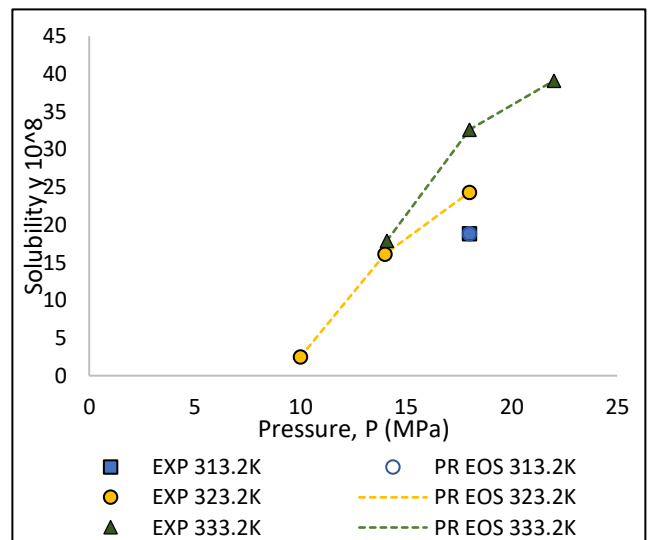
(a)



(b)

FIGURE 4 Solubility of 6-methoxyflavone at 313.2K, 323.2K and 333.2K without co-solvent (a) and comparison of experimental data and predicted data of 6-methoxyflavone solubility at 313.2K with co-solvent (b)

The figure indicates that the 6-methoxyflavone solubility increases when pressure increases. The solubility of 6-methoxyflavone shows the highest at 20MPa. There is a significant difference of solubility with the presence of co-solvent and without co-solvent. Figure 4(b) shows that co-solvent helps improve the efficiency of supercritical fluid extraction by enhancing the solubility of 6-methoxyflavone by increasing the polarity. It can be expected that the effect of co-solvent will increase the yield of natural extract due to co-extraction of less polar and polar compound.



(a)

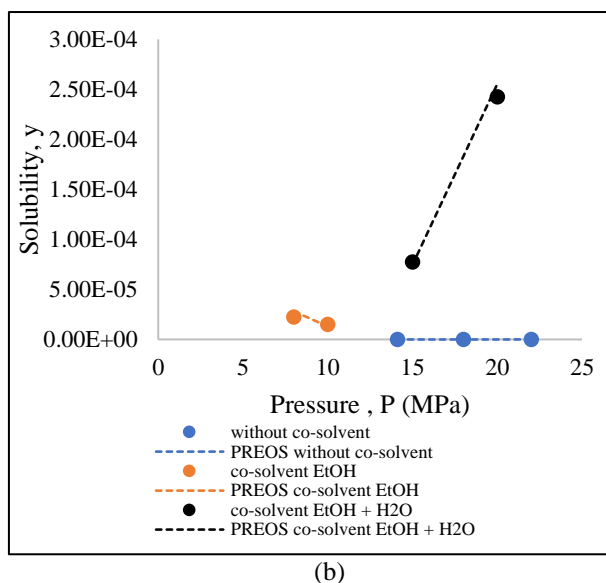


FIGURE 5 Solubility of 7-hydroxyflavone at 313.2K, 323.2K and 333.2K without co-solvent (a) and comparison of experimental data and predicted data of 7-hydroxyflavone solubility at 333.2K (b)

Figure 5(a) shows the comparison of predicted data with application of PR EOS and experimental data of 7-hydroxyflavone solubility in 313.2K, 323.2K and 333.2K. The figure indicates that 7-hydroxyflavone solubility increases when pressure increases. Solubility of 7-hydroxyflavone shows the highest at 20MPa. There is a significant difference of solubility with the presence of co-solvent and without co-solvent. Figure 5(b) shows that cosolvent helps to improve the efficiency of supercritical fluid extraction by enhancing the solubility of 7-hydroxyflavone by increasing the polarity. Water, methanol and ethanol contain hydroxyl group that is able to form hydrogen bond with cosolvent. Water contains shorter chain and higher polarity, making flavonoid more likely to be polar. This proves the difference in solubility flavonoids with the presence of co-solvent.

#### Solubility data comparison of flavonoid using ternary phase diagram

The presence of cosolvent enhances the solubility of the flavonoids. The quaternary phase VLE of CO<sub>2</sub> (1) – ethanol (2) – water (3) – flavonoid (4) is identified in Table 10-12. In this work, the VLE data of CO<sub>2</sub>, ethanol and water is used to compare the solubility performance of flavone, 6-methoxyflavone and 7-hydroxyflavone. Figure 6 shows the ternary phase diagram of CO<sub>2</sub> (1) – ethanol (2) – water (3) at 313.2K and 10 MPa. The results shows that the mole fraction of all three components have a slight reduction with the presence of flavonoid. Comparing the 3 flavonoids, 7-hydroxyflavone shows a relatively higher mole fraction of ethanol and water compared to 6-methoxyflavone and flavone. This results in the lower solubility of 7-hydroxyflavone as compared to 6-methoxyflavone and flavone. The solubility of flavone is higher than 6-methoxyflavone and Sato et al. (2019) [9] has proved that 7-

hydroxyflavone has the lowest solubility. The structural difference may result in the difference in polarity when cosolvent is added.

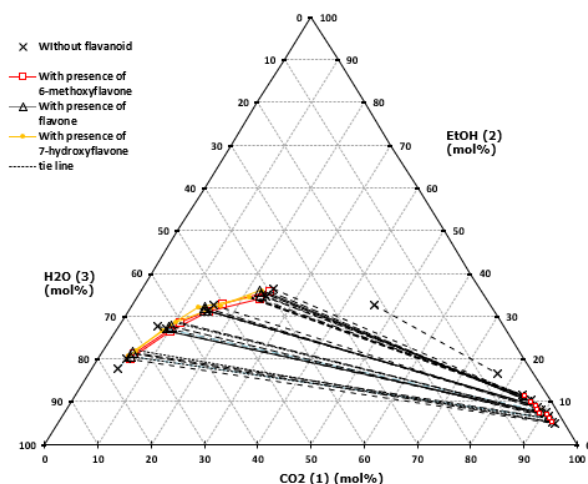


FIGURE 5 Ternary diagram of CO<sub>2</sub>(1) – ethanol(2) – water(3) at 313.2K and 10 MPa

## 5. Conclusion

Vapor–liquid equilibrium (VLE) modeling of CO<sub>2</sub> (1) – ethanol (2) – water (3) – flavonoid (4) mixture has been investigated with the application of PR EOS. The binary interaction parameter  $k_{ij}$  was regressed at minimum average absolute relative deviation (AARD%) of 5.1%. Ternary diagrams were plotted to show the data accuracy by comparing the experimental and predicted data. The effects of cosolvent on solubility of flavone, 6-methoxyflavone and 7-hydroxyflavone are compared. Ternary phase diagram of VLE with or without flavonoid is plotted to compare the best soluble flavonoid with supercritical carbon dioxide extraction with the presence of co-solvent

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