turnitin **Turnitin Originality Report**

51 Investigation on Supercritical CO2 Extraction of Black Nightshade Berries by Shella Santoso

From Similarity check (check paper Jakad SPS)

Processed on 01-Mar-2022 10:00 WIB
ID: 1773487007
Word Count: 7446

Similarity Index	Similarity by Source	
17%	Internet Sources:	N/A
	Publications:	17%
	Student Papers:	N/A

sources:

1 3% match (publications)
Astrid Rahmawati, Debora Pang, Yi-Hsu Ju, Felycia Edi Soetaredjo, Ong Lu Ki, Suryadi Ismadji. " Supercritical CO Extraction of Phytochemical Compounds from Mimosa pudica Linn ", Chemical Engineering Communications, 2014

2 1% match (publications)
Patrícia Coimbra, Miguel R. Blanco, Hélio S. R. Costa Silva, Maria H. Gil, Hermínio C. de Sousa. "Experimental Determination and Correlation of Artemisinin's Solubility in Supercritical Carbon Dioxide", Journal of Chemical & Engineering Data, 2006

3 1% match (publications)
Jiaqi Luo, Xintong Yao, Olugbenga P. Soladoye, Yuhao Zhang, Yu Fu. "Phosphorylation modification of collagen peptides from fish bone enhances their calcium-chelating and antioxidant activity", LWT, 2022

4 1% match (publications)
Syntia Lukmanto, Natalia Roesdiyono, Yi-Hsu Ju, Nani Indraswati, Felycia Edi Soetaredjo, Suryadi Ismadji. " SUPERCRITICAL CO EXTRACTION OF PHENOLIC COMPOUNDS IN ROSELLE (L.) ", Chemical Engineering Communications, 2013

5 1% match (publications)
Yu-Chiao Yang, Ming-Chi Wei. "Ethanol solution-modified supercritical carbon dioxide extraction of triterpenic acids from Hedyotis corymbosa with ultrasound assistance and determination of their solubilities", Separation and Purification Technology, 2015

6 1% match (publications)
Food Engineering Series, 2015.

7 1% match (publications)
Lara Čižmek, Mojca Bavcon Kralj, Rozelindra Čož-Rakovac, Dmitrii Mazur et al. "Supercritical Carbon Dioxide Extraction of Four Medicinal Mediterranean Plants: Investigation of Chemical Composition and Antioxidant Activity", Molecules, 2021

8 1% match (publications)
Nutrition & Food Science, Volume 40, Issue 4 (2010-07-31)

9 1% match (publications)
Yu Dong, Tiantian Ping, Shufeng Shen. "Solubility of CO2 in nonaqueous system of 2-(butylamino)ethanol with 2-butoxyethanol: Experimental data and model representation", Chinese Journal of Chemical Engineering, 2021

10 < 1% match (publications)

Patrícia Coimbra, Miguel R. Blanco, Hélio S. R. Costa Silva, Maria H. Gil, Hermínio C. de Sousa. "Experimental Determination and Correlation of Artemisinin's Solubility in Supercritical Carbon Dioxide", Journal of Chemical & Engineering Data, 2006

11 < 1% match (publications)

Inês J. Seabra, Mara Elga M. Braga, Maria Teresa Batista, Hermínio C. de Sousa. "Effect of solvent (CO2/ethanol/H2O) on the fractionated enhanced solvent extraction of anthocyanins from elderberry pomace", The Journal of Supercritical Fluids, 2010

12 < 1% match (publications)

Jingwei Chen, Tian Meng, Erwei Leng, Jiaqiang E. "Review on metal dissolution characteristics and harmful metals recovery from electronic wastes by supercritical water", Journal of Hazardous Materials, 2022

13 < 1% match (publications)

Nittaya Ngamkhae, Orawan Monthakantirat, Yaowared Chulikhit, Chantana Boonyarat et al. "Optimization of Extraction Method for Kleeb Bua Daeng Formula and Comparison between Ultrasound-Assisted and Microwave-Assisted Extraction", Journal of Applied Research on Medicinal and Aromatic Plants, 2022

14 < 1% match (publications)

Kurabachew Simon Duba, Luca Fiori. "Solubility of grape seed oil in supercritical CO2: Experiments and modeling", The Journal of Chemical Thermodynamics, 2016

15 < 1% match (publications)

Xinxi Zhang, Xian Lu, Sheng Li, Meiying Zhong, Xiaodong Shi, Gang Luo, Lei Ding. "Investigation of 2,4-dichlorophenoxyacetic acid adsorption onto MIEX resin: Optimization using response surface methodology", Journal of the Taiwan Institute of Chemical Engineers, 2014

16 < 1% match (publications)

Mandana Bimakr, Russly Abdul Rahman, Farah Saleena Taip, Noranizan Mohd Adzahan, Md. Zaidul Islam Sarker, Ali Ganjloo. "Optimization of Ultrasound-Assisted Extraction of Crude Oil from Winter Melon (Benincasa hispida) Seed Using Response Surface Methodology and Evaluation of Its Antioxidant Activity, Total Phenolic Content and Fatty Acid Composition", Molecules, 2012

17 < 1% match (publications)

S. Ismadji, A. Kurniawan, Y.H. Ju, F.E. Soetaredjo, A. Ayucitra, L.K. Ong. "Solubility of azadirachtin and several triterpenoid compounds extracted from neem seed kernel in supercritical CO2", Fluid Phase Equilibria, 2012

18 < 1% match (publications)

Shella Permatasari Santoso, Artik Elisa Angkawijaya, Alfin Kurniawan, Maria Yuliana et al. "Utilization of Nanocrystalline Cellulose for Adsorption of Divalent Cobalt Ions in the Aqueous Phase", Fine Chemical Engineering, 2020

19 < 1% match (publications)

M. Khayet, M.N. Abu Seman, N. Hilal. "Response surface modeling and optimization of composite nanofiltration modified membranes", Journal of Membrane Science, 2010

20 < 1% match (publications)

Shabnam Sepahpour, Jinap Selamat, Mohd Abdul Manap, Alfi Khatib, Ahmad Abdull Razis. "Comparative Analysis of Chemical Composition, Antioxidant Activity and Quantitative Characterization of Some Phenolic Compounds in Selected Herbs and Spices in Different Solvent Extraction Systems", Molecules, 2018

---

21 < 1% match (publications)

Majid Sharifi-Rad, Francesco Epifano, Serena Fiorito, José M. Álvarez-Suarez. "Phytochemical Analysis and Biological Investigation of Nepeta juncea Benth. Different Extracts", Plants, 2020

---

22 < 1% match (publications)

Bruno Rodrigues Wenceslau, Kátia Andressa Santos, Edson Antonio da Silva, Lúcio Cardozo-Filho et al. "Guariroba (Syagrus oleracea) kernel oil extraction using supercritical CO2 and compressed propane and its characterization", The Journal of Supercritical Fluids, 2021

---

23 < 1% match (publications)

Chenling Qu, Songcheng Yu, Li Luo, Yan Zhao, Yawei Huang. "Optimization of ultrasonic extraction of polysaccharides from Ziziphus jujubaMill. by response surface methodology", Chemistry Central Journal, 2013

---

24 < 1% match (publications)

Su Bin Hyun, Sungmin Bae, Chang-Gu Hyun. "Antioxidant Activities of Jeju Wax Apple (Syzygium samarangense) and Safety of Human Keratinocytes and Primary Skin Irritation Test", Cosmetics, 2020

---

25 < 1% match (publications)

Zijian Liang, Vivi Veronica, Jiehe Huang, Pangzhen Zhang, Zhongxiang Fang. "Combined effects of plant food processing by-products and high oxygen modified atmosphere packaging on the storage stability of beef patties", Food Control, 2022

---

26 < 1% match (publications)

Anbarasi Karunanithi, Sivakumar Venkatachalam, Jeeva Senrayan. " Influence of ultrasonic waves and conventional extraction methods on phenolic compound yield and phytochemical composition from L. peel ", International Journal of Food Engineering, 2021

---

27 < 1% match (publications)

Food Engineering Series, 2011.

---

28 < 1% match (publications)

John Shi, Gauri Mittal, Erin Kim, Sophia Jun Xue. " Solubility of Carotenoids in Supercritical CO ", Food Reviews International, 2007

---

29 < 1% match (publications)

Khayet, Mohamed, Cornel Cojocaru, and Carmen García-Payo. "Application of Response Surface Methodology and Experimental Design in Direct Contact Membrane Distillation", Industrial & Engineering Chemistry Research, 2007.

---

30 < 1% match (publications)

Snežana Filip, Branimir Pavlić, Senka Vidović, Jelena Vladić, Zoran Zeković. "Optimization of Microwave-Assisted Extraction of Polyphenolic Compounds from Ocimum basilicum by Response Surface Methodology", Food Analytical Methods, 2017

---

31 < 1% match (publications)
Tan, I.A.W.. "Preparation of activated carbon from coconut husk: Optimization study on removal of 2,4,6-trichlorophenol using response surface methodology", Journal of Hazardous Materials, 20080501

paper text:

Article Volume 11, Issue 5, 2021, 13502 - 13515 https://doi.org/10.33263/BRIAC115.1350213515 Investigation on Supercritical CO2 Extraction of Black Nightshade Berries (Solanum nigrum Linn.) Reinard Dona Tiono 1 ,

18**Shella Permatasari Santoso 1,2,* , Artik Elisa Angkawijaya 3 , Maria Yuliana 1** , Jindrayani Nyoo Putro **1**

, Jenni Lie 2 ,

18**Felycia Edi Soetaredjo 1,2** , Wenny Irawaty 1 , **Suryadi Ismadji 1,2**

1 Department of Chemical Engineering, Widya Mandala Surabaya Catholic University, Surabaya 60114, East Java, Indonesia 2 Department of Chemical Engineering, National Taiwan University of Science and Technology, Taipei 10607, Taiwan 3 Graduate Institute of Applied Science and Technology, National Taiwan University of Science and Technology, Taipei 10607, Taiwan * Correspondence: shella_p5@yahoo.com; Scopus Author ID 55701829300 Received: 9.01.2021; Revised: 4.02.2021; Accepted: 7.02.2021; Published: 13.02.2021 Abstract: A set of supercritical extractions (SCE) using carbon dioxide (CO2) has been performed on Solanum nigrum Linn. A

1**design of experiment (DoE**) using Box-Behnken **was** applied **to investigate the**

influential parameters on SCE. The relationship between extraction parameters (i.e., temperature, time, and pressure) and extraction products (i.e., phenolics-TPC, alkaloids-TAC, and flavonoids-TFC) was evaluated. It was found that temperature and pressure are the most influencing parameters in the SCE. Both give a synergistic effect in increasing the extraction yield. The optimum SCE conditions are 333 K, 30 min, and 240 bar; with extraction, yields expressed as TPC, TFC, and TAC are 55.1677

13**mg GAE/g extract**, 28.0308 **mg QE/g extract**, and 5.9460 **mg** HYE/**g extract**

, respectively. Solubility data correlations were done by using Chrastil's model. The adjustable parameters of Chrastil's model were found to be consistent with their physical meaning and can be applied in the SCE of Solanum nigrum Linn. Keywords: Solanum nigrum; box behnken; supercritical extraction; chrastil; optimization. © 2021 by the authors.

 1. Introduction

Solanum nigrum Linn. (SNL) is a bushy tropical-weed plant with berries, native from Eurasia. SNL berries are potentially toxic, especially when unripe; the risk of poisoning causes SNL utilization to be sparse. Aside from their toxicity, proper treatment of the mature SNL berries can provide beneficial therapeutic effects. This is since SNL berries contain bioactive compounds that show anti-diabetic, anti-oxidant, anti-tumor, anti-cancer, and anti- inflammatory [1-3]. Several studies have been conducted to examine the biological activity of the SNL plant extracts. Chen and co-workers showed that acetic acid-methanol extract of SNL has parasitemia suppression activity [4]. Some studies reported that SNL extract possesses a cytotoxic activity to several cell lines such as HL-60, Jurkat, Hep3B, and HepJ5.3 [5, 6]. The investigation by Patel et al. (2014) showed that chloroform extract of SNL gives active compounds that can inhibit mucositis [5]. Cyclohexane-methanol extract of SNL contains steroidal saponins with anti-inflammatory activity [6]. Furthermore, aqueous extracts of SNL show anti-diabetic activity [7]. The application of green extraction using supercritical fluids for extracting the pharmacologically active compounds from SNL has not been documented to date. Supercritical extraction (SCE) is considered more environmentally friendly than other extraction methods, e.g., solvent-mediated extraction, microwave-assisted extraction (MAE), and sonication-assisted extraction (SAE) [8-10]. The conventional solvent-mediated extraction is indeed unsuitable for the extraction of phytochemicals due to the inefficient and high risk of thermal degradation. Also, using a large volume of organic solvents raises pollution problems in the surrounding environment. It requires costly post-extraction stages to obtain high purity and safe-consumed products. SAE and MAE techniques are both superior to the conventional solvent-mediated method in terms of extraction period and performance, in addition to lower risk of thermal degradation [11-13]. However, the use of organic solvent and its following purification stages can introduce a high level of contamination into the product, which can be detrimental for biological applications. SCE has gained increasing attention and is an up-and-coming technique for isolating various active phytochemicals from the plant matrices. The merits of SCE (which make this method expeditious and straightforward) emerge from its short extraction time, high precision, and flexible application due to the possibility of continuous modulation of the solvent power by manipulating pressure and temperature [11, 12, 14-17]. Further advantage coming from the recyclability of the extraction solvent. Thus it can significantly reduce the operating costs and minimize waste generation. Among the supercritical solvents, carbon dioxide (CO_2) is the most notable owing to its moderate critical temperature and pressure (304.25 K and 7.38 MPa, respectively), very low toxicity, safe handling, and storage, inexpensive, and easily obtained in ultra-high purity [18-20]. The present study aims to optimize the SCE using CO_2 as a solvent towards pharmacologically active compounds existing in SNL berries. There is no study dealing with the SCE of active compounds in SNL to the best of our knowledge. Parameter optimization and correlation were conducted using the response surface method —Box-Behnken design (BBD). The SCE parameters including temperature, pressure, and time were optimized towards

1**the total** alkaloid **content (TPC), total flavonoid content (TFC), and total**

phenolic content (TPC) of the resulting extracts. The amount of alkaloid and phenolic compounds dissolved in CO_2 can be assumed as the solubility of natural active compounds extracted by supercritical CO_2. This information is critical for designing and optimizing scale-up extraction processes. The equilibrium solubility data was modeled using Chrastil density-based equations. 2. Materials and Methods 2.1. Materials. The whole plant of SNL was purchased from a distribution agent of PT. Supra Boga Lestari, Surabaya, East Java, Indonesia. The SNL was harvested from the plantation in Pangalengan (7.1989° S, 107.5505° E), West Java. Ultra-high-purity grade CO_2 (99.995% purity) was purchased from PT Aneka Gas Industri, Sidoarjo, East Java, Indonesia. Absolute

1**ethanol (99**.8%) **and Folin-Ciocalteu** (F-C) **reagent were** purchased from **Merck (Darmstadt, Germany**). Standard **gallic acid (98**

%), 1,1-diphenyl-2-picrylhydrazyl (DPPH), Bromo cresol Green (dye content 95%), L-hyoscyamine (98%), vitexin (95%), quercetin dihydrate (98%), and potassium acetate (98%) were obtained

> 9**from Sigma-Aldrich**, Singapore. **All** the **chemicals were used as received without further purification**

. All solutions were prepared with distilled water

> 25**obtained from a Millipore Milli-Q water purification system**

(specific resistivity of 18.2 MΩ·cm). 2.2. Supercritical extraction (SCE) of SNL berries. Before the extraction, the SNL berries were removed from the stem and repeatedly washed with tap water to remove surface dirt and dried in an oven at 40 °C for at least

> 1**48 h until the moisture content was** reduced to 6.**5%. The** dried SNL was **then crushed** and sieved **using a**

Retsch AS 200 sieve shaker (Retsch GmbH) and the fraction retained on the +/- 70 mesh sieve was collected and weighed. Finally, the SNL powder was stored in an airtight plastic container before SCE experiments. The SCE of dried SNL berries was carried out using a laboratory-scale supercritical fluid extraction apparatus, which comprised of

> 4**a high-pressure** metering **pump (Eldex AA-100- S-2-CE, USA**

) that can dispense flow rates between 0.2 and 10 mL/min,

> 1**a pressure transducer (Druck PTX-611**

, 0.1-700 bar), a temperature-controlled oven (Memmert UNB 500) for heating the system,

> 22**and a stainless steel** high-pressure reactor **with an internal volume of** ~150 **cm3. The**

maximum operating pressure, temperature, and flow rate of the extraction system were 400 bar, 300 °C, and 10 mL/min, respectively. Briefly, 20 g of SNL powder was placed in the extraction vessel, and cotton wool was packed at both ends of the cell to prevent solid particles' carryover into the tubing and clogging the system. The extraction cell was then placed in the heating chamber and heated to the desired temperature. Subsequently, liquid CO2 was pumped into the system by a high-pressure metering pump at a rate of 10 cm3/min until the target pressure was reached. The supercritical extraction was performed under varied pressures of 80-240 bar and temperatures of 40-60 °C. After the desired conditions were achieved, the static extraction (CO2 flow stopped) was started until the equilibrium condition of extraction was met (2h). Separation of the bioactive compounds from CO2 was performed by using liquid solvent trapping. In such a

trapping system, the extracts were recovered by bubbling CO2 into a collection flask containing 10 mL of 99.8% v/v ethanol at ambient temperature.

> 11**A trap was used to prevent any losses with the expanded CO2, whose flow was measured by a wet gas meter**

. During the decompression of CO2, the transfer tube was gently heated to prevent the non-volatile analytes' precipitation. Ethanol was used to collect the bioactive extract. The bioactive extract- containing ethanol was kept in amber bottles

> 30**and stored at 4°C until further analysis**

. All

> 15**experiments were carried out** at least duplicated, **and the average values** of **the**

yield and measurements were reported. 2.3. Characterization of the

> 20**extracts by** HPLC. **High-performance liquid chromatography (HPLC**) analysis **was** conducted to determine **the**

phenolic, flavonoid, and alkaloid compounds present in SNL extracts. The HPLC system consisted of a JASCO chromatograph equipped with a quaternary gradient pump (PU- 2089 Plus),

> 17**a JASCO** type **UV-2077 Plus** variable-wavelength **UV-Vis detector and** an **LC-NetII/ADC** hardware interface. **The** separation **was**

achieved on an Enduro C18 column (250

> 11**mm×4.6 mm, 5 µm**

) thermostated at 30 °C with mobile phases consisting of solvent A (water/acetic acid, 97:3, v/v) and solvent B (acetonitrile/acetic acid, 97:3, v/v). The injection volume was 5 µL with the mobile phase flow rate of 1 mL/min. The following gradient elution program was employed to separate the major components of bioactive compounds from the column: 0 min 90% solvent A; 0 to 15 min solvent A from 90 to 80%; 15 to 38 min solvent A from 80 to 68%; 38 to 50 min solvent A from 68 to 54%; 50 to 55 min solvent A from 54 to 45%; 55 to 60 min solvent A from 45% to 0; and 60 to 70 min solvent A from 0 to 90%. Before each injection, the chromatographic system was equilibrated for at least 15 min. Identification of chromatographic peaks corresponding to bioactive compounds in SNL extracts was conducted

5by comparing the retention times and the UV spectra of the peaks in the samples' chromatograms with those of standards

. Data processing was made using the ChromNAV software package (Version 1.18.04, Jasco Corp., Tokyo, Japan). 2.4.

13Determination of total phenolic content (TPC). The TPC of SNL extract was determined using the Folin-Ciocalteu

(F-C) assay following the procedure described by Habila et al. (2010) and Cavalcanti et al. (2012) with a slight modification [12, 21, 22]. Briefly, 2 mL of the diluted

1Folin-Ciocalteu reagent (1:10; v/v) was added to 1 mL of

SNL extracts and

25incubated for 5 min at room temperature. Subsequently, 2 mL of

Na2CO3 solution (7.5%, w/v) solution was added, and the mixture was kept in the dark for 60 min at room temperature. The absorbance at 765 nm was measured on a Shimadzu UV-1700 PharmaSpec UV-Vis spectrophotometer (Shimadzu Corp., Japan) against a blank containing distilled water instead of sample extract.

24Gallic acid was used as a standard for the determination of

TPC. The results are expressed as gallic acid equivalents (GAE) using a standard gallic acid curve prepared with a series of gallic acid (0, 5, 10, 20, 40, 60, 80, and 100 μg/mL). The measurements were

16performed in triplicate, and the mean values were reported. The TPC (mg GAE/g

SNL) was calculated according to equation (1): **Rdad (kkdL)×000** TPC = (1) **Rakkkd wdddds (d)** 2.5. Determination of

1total flavonoid content (TFC). The TFC was determined by the aluminum chloride colorimetric method, as previously described by Woisky and Salatino (1998

) with slight modifications [23-25]. Briefly, an aliquot of 0.5 mL of SNL extract was mixed with

8**0.1 mL of 10**% (w/v) **aluminum chloride, 0.1 mL of potassium acetate** (0.1 M), **and 2.8 mL of distilled water. The reaction mixture was** then **allowed to stand at room temperature for 30 min**. After 30 min, **the** reaction mixture's **absorbance**

21**was recorded at 415 nm using a UV-Vis spectrophotometer. The** TFC **was calculated from a calibration curve** of **quercetin**

(0-100 μg/mL). The results are expressed as milligram of quercetin equivalent per gram dry weight of SNL (mg QE/g SNL). 2.6. Determination of total alkaloid content (TAC). The TAC of SNL extract was determined by a titrimetric method based on the complex formation between alkaloid and bromocresol green. In a typical procedure, one

1**mL of** SNL **extract was dissolved in 2.0 mL** acetone **and** 10.0 **mL** ether. **The**

mixtures were transferred to a 250 mL volumetric flask, followed by the addition of 5 mL bromocresol green solution. The bromocresol green solution was prepared

27**following the procedure described by et al. The**

1**mixture was** then **titrated with 0.005 N H2SO4 until the appearance of light green color** (endpoint). **Each** mL **of acid used is equivalent to** 7.25 mg **of alkaloid calculated as hyoscyamine**

equivalent (HYE). The percent total alkaloid was calculated by the following equation: % Alkaloid = **Wddddskd Akkakkdd** ×100% (2) **Rdd wddddskd sdd kkaks sakkkd** 3. Results and Discussion 3.1. Experimental design in SCE of SNL berries. Major bioactive compounds, specifically phenolic, flavonoid, and alkaloid, were identified from the crude extract of SNL by using the HPLC chromatography analysis and were quantified as TPC, TFC, and TAC, respectively.

19**The response surface methodology (RSM) involves** the **statistical design of experiments** where **all factors are varied together over a set of experimental runs**

, which can be used

15**to develop, improve, and optimize processes**

[26-30]. This technique has been applied in many areas of applied physics and engineering to reduce the cost of expensive analysis methods and their associated numerical noise. A computer software, namely

Minitab 19.2. (Minitab Inc., PA, USA), was used to design the experimental matrix and to perform the necessary statistical analyses. For the experimental design,

23**a three- variable three-level Box-Behnken design (BBD) was** applied **to optimize the extraction conditions for** obtaining high recovery **of**

bioactive compounds from SNL powder. The factors considered for experimental design are the extraction temperature (K, X1), extraction time (min, X2), and pressure (bar, X3), where each factor was set at three levels, thus generating a total of 15 experimental runs as shown in Table 1.

16**Table 1. Experimental design (coded and uncoded levels) and results of** the **response variable**

. No. X1 X2 X3 TPCa TFCb TAC c 1 313 30 240 9.84 7.10 2.44 2 313 30 80 2.95 1.37 0.55 3 313 75 160 7.95 5.25 1.55 4 313 120 240 8.98 6.38 2.08 5 313 120 80 2.05 1.45 0.59 6 323 30 160 17.78 8.58 2.65 7 323 75 240 25.8 13.08 3.67 8 323 75 160 17.15 8.62 2.73 9 323 75 80 3.17 1.42 0.59 10 323 120 160 17.6 8.69 2.77 11 333 30 240 59.01 30.21 6.30 12 333 30 80 7.78 2.28 0.97 13 333 75 160 7.07 2.09 0.92 14 333 120 240 57.95 29.57 6.15 15 333 120 80 6.95 2.14 0.96 a Phenolics extract expressed as mg gallic acid equivalent/g extract b Flavonoids extract expressed as mg quercetin equivalent/g extract c Alkaloids extract

7**expressed as mg** hyoscyamine **equivalent/g extract**

Extraction time, X2, is an essential factor in the economic issue and risk of product degradation. Ye and Lai (2012), in the optimization of SCE conditions of onion oil using RSM, found the

30**linear and quadratic terms of extraction time**

significantly affected the oil recovery [31]. In this study, a second-order polynomial regression model was developed to express the relationship between the response and the coded independent variables as follows: Y =ko +?kiXi +?kiiXi2 +??kijXiXj n n n n

29**i =1 i =1 i** =1 **j** =1 (3) **where Y denotes the predicted response of the process**

, which in this case corresponds to TPC, TFC, and TAC, Xi refers to the coded levels of the factors (or independent variables), and k0, ki, kii, and kij are the constant, linear, quadratic, and interaction coefficients, respectively. The coded and uncoded values of the independent variables used in the RSM design are presented in Table

31**1. The experimental sequence was randomized to minimize the effects of the uncontrolled factors. The**

analysis of variance (ANOVA) was further employed to evaluate the credibility of the model response and the contribution of the linear, quadratic, and interaction terms to the response variable at the 5% significance

level. The results are presented in Table 2. The response surface model's positive and negative coefficient values indicate synergistic and antagonistic effects between the corresponding independent variable and the response, respectively. From Table 2, the particular effects and

1**interaction effect of pressure with temperature** were highly **significant in the case of TPC**

, TFC, and TAC of SNL extract, as indicated from P-values less than < 0.05. The small P-value (<0.05) indicates the more significant effect on the several response variables. On the other hand, the individual variables and their interaction forms gave insignificant effects

26**on the yield of TPC, TFC, and TAC**

(P- value > 0.05). By neglecting the coefficients of the non-significant (P > 0.05) terms, the model equations for YTPC, YTFC, and YTAC can be expressed as follows: YTPC = –3155 + 20.8X1 – 0.50X2 – 4.47X3 – 0.0339X12 + 0.00335X22 + 0.000560X32 – 0.00004X1X2 + 0.01381X1X3 – 0.000007X2X3 (4) YTFC = –1348 + 9.1X1 – 0.024X2 – 2.259X3 – 0.0151X12 + 0.00171X22 + 0.000324X32 – 0.00004X1X2 + 0.00698X1X3 – 0.000045X2X3 (5) YTAC = –762 + 4.50X1 – 0.02X2 + 0.325X3 – 0.00655X12 + 0.000449X22 + 0.000037X32 – 0.00016X1X2 – 0.001116X1X3 + 0.000022X2X3 (6) Table

15**2. Analysis of variance** for **the** factors in **the response surface model**

. Source DF TPC TFC TAC F P F P F P Model 9 6.53 0.03 5.53 0.04 6.34 0.03 Linear 3 14.14 0.01 11.98 0.01 15.17 0.01 X1 1 15.82 0.01 8.95 0.03 8.42 0.03 X2 1 0.02 0.89 0.01 0.93 0.02 0.90 X3 1 26.58 0.01 26.99 0.01 37.08 0.01 Square 3 0.95 0.48 0.87 0.51 1.09 0.44 X12 1 0.41 0.55 0.26 0.63 1.42 0.29 X22 1 1.64 0.26 1.38 0.29 2.22 0.20 X32 1 0.46 0.53 0.49 0.51 0.19 0.68 Two-way 3 4.50 0.07 3.73 0.10 2.75 0.15 X1 X2 1 0.00 0.10 0.00 0.99 0.00 0.95 X1 X3* 1 13.50 0.01 11.17 0.02 8.20 0.04 X2 X3 1 0.00 0.99 0.01 0.93 0.05 0.84 *The significant parameters in the SCE process of SNL F and P represent the F-value and P-value, respectively The R2 values obtained for the model equations of YTPC, YTFC, and YTAC are 0.9216, 0.9087, and 0.9194, respectively. Furthermore, based on F-value and P-value (Table 2), one can see that the interaction between temperature (X1) and pressure (X3) has a synergistic effect, while the linear term of temperature, extraction time, and pressure all have antagonistic effects. Figure 1 depicts the optimum condition of each significant parameter in supercritical fluid extraction of TPC, TFC, and TAC from SNL. The

28**optimum conditions for supercritical fluid extraction**

(within the SNL investigated conditions) are 333 K, 30 min, and 80 bar. The optimum

1**TPC, TFC, and TAC** yields **were** 55.1677 **mg GAE/g**

extract (0.93254 precision), 28.0308 mg QE/g extract (0.92444 precision), and 5.9460 mg HYE/g extract (0.93843 precision), respectively. Figure 1. Optimization plot of extraction parameters of temperature (K), time (minute), and pressure (bar). The extraction yield and data precision are presented in y and d, respectively. Primarily, temperature and pressure are the crucial factors influencing the yield of target compounds in supercritical fluid extraction, strongly related to

28**the solvating power of fluids in the supercritical phase**

[32, 33]. In this regard, the pressure affected the density of CO2, while temperature affected the vapor pressure and diffusivity of target compounds. Since the dissolving power of supercritical CO2 is directly related to the CO2 density, an increase in

5**pressure at a constant temperature** allows **higher** extraction efficiency **of**

bioactive compounds as a result of enhanced. In contrast, the density of CO2 decreased with temperature, which

14**has a negative effect on the** density of CO2. **The density**

and viscosity of CO2 decreased

12**with the increase of temperature. The** decrease in **viscosity**

with an increase in temperature significantly influences the mobility of CO2 in the inner matrix of a solid; it will easily penetrate and reach the internal interior of the solid matrix. Therefore, a combination of pressure and temperature is the most important factor in the supercritical fluid extraction processes. The parameters that significantly affected the process also can be examined using the Pareto chart. The Pareto chart, Figure 2, shows the significance of the investigated extraction parameters to the yield of TPC, TFC, and TAC. It is identified that pressure and temperature are the influential parameters on TPC, TFC, and TAC yield, while extraction time was not a significant factor ($P > 0.05$). The increase of the yield with the rise in pressure is because of the enhanced density and solvent capacity of CO2 as the extraction solvent. Figure 2. Pareto chart showing the effect of SCE parameters on the yield of TPC, TFC, and TAC. The optimization study shows that temperature and pressure have a significant and synergistic effect in increasing the yield of SCE of SNL. The surface plot (Figure 3) shows that the

12**increase of pressure and** temperature supports **the increase of** TPC, TFC, **and** TAC yield. **The** enhancement **effect**

can be correlated with an increase in the solute's volatility, which facilitates its dissolution [34, 35]. However, increasing temperature (only) while maintaining pressure at 80 bars does not significantly enhance the extraction yield. Figure 3. Surface plot showing the effect of SCE pressure and time on the yield of TPC, TFC, and TAC. 3.2. Correlation of the TPC, TFC, and TAC by density-based model. As previously mentioned in the response surface method-BBD analysis, the combination of pressure and temperature was the most crucial factor in the SCE of bioactive compounds from SNL berries. The extraction efficiency in terms of TPC, TFC, and TAC yields

4**increased with the increase** in **temperature and pressure**. Although **the**

SCE

2**proved to be a promising alternative to extract** bioactive compounds **from** plant materials, **the**

supercritical technology is considered unfavorable due to high operational costs and the process's requirement to be operated at high pressures with exact process control. The accurate knowledge of solids' equilibrium solubility data in supercritical CO2

14**in a wide range of temperature and pressure** is crucial **for**

designing supercritical extraction processes [36-38]. In most cases, these solubility data

2**are not easy to predict because** of the **lack of** reliable **models**

for predicting solid equilibrium solubility in supercritical fluids and limited information on the physical parameter necessary for those available models [39, 40]. Therefore, modeling and correlation are required to develop a mathematical model that can describe the system based on a limited number of existing experimental data. Many mathematical

6**models have been** developed **to** predict **the phase behavior of** solid- supercritical fluid **systems**

[41, 42]. These models can also provide valuable context for understanding the dissolution phenomenon and can be used to predict solute solubility in supercritical CO2 at desired pressures and temperatures. In this case, some of the developed models are purely empirical, although some may have a fundamental thermodynamic basis. A cluster analysis,

6**density-based method, is an empirical or semi-empirical approach** that **relies on developing a relationship between a** solid **solute**'s solubility **and the density of**

supercritical fluid

2**based on** the **simple error minimization using** the **least-squares** method. **The** correlation **of**

solids' solubility in supercritical CO2 based on density-based models provides a more straightforward way than the equations of state (EoS)-based models because it does not require

2**critical and thermophysical properties of the involved**

solid [43]. Chrastil (1982) derived a density-based model by correlating

1**solids and liquids**' solubility **in supercritical gases**

10**based on the supposition that one molecule of solute A** associated **with k molecules of solvent B to form a solvate complex ABk in equilibrium with the system**

[35, 44-46]. This model has been widely applied to model solid solubility of phenolic compounds derived from natural matrices in supercritical CO2 with satisfactory correlation results [47, 48]. Chrastil's model has linear (Eq. 7) and non-linear (Eq. 8) forms as follows: ln Y = k ln ? + ? T + ? (7) Y = ? k exp (? / T + ?) (8) In the above expressions, Y is the solid solubility in a supercritical fluid or the number of bioactive compounds extracted from SNL by SCE (

5**g/L), ? is the density of CO2 (g/L), T is the** extraction **temperature (K**), k **is** the **association number**

, ? is a constant account to the heat

2**of vaporization and solvation of the solute** related to **the**

set temperature. For simplification purposes, the mixtures of phenolics, flavonoids, and alkaloids present in the supercritical extracts were quantified as gallic acid, quercetin, and hyoscyamine equivalent, respectively. The density of

4**CO2 at various temperatures and pressures** was determined by **the Peng-Robinson**

EoS, while the

14**adjustable parameters k, ?, and ? of the Chrastil' model**

were obtained by non-linear least-squares fitting of experimental data. Figure 4 shows 3D scatter plots of experimental data (

26**the extraction yield**) in terms **of TPC, TFC, and TAC**

17**as a function of** CO2 **density and temperature. The**

corresponding Chrastil's model fits. The experimental data are denoted by solid circles, while the 3D wireframe plots represent non-linear least-squares model fits experimental data. It is shown that extracts started to emerge as a specific CO2 density was reached 200 g/L, and at higher temperatures, the extract

can be obtained more. A similar phenomenon is also observed in other SCE related researches [45, 49, 50]. These results exhibited that the analyte's constant CO2 density, temperature, and vapor pressure have a parallel effect.

6**The increase in temperature causes** an increase in **the** analyte's **vapor pressure**, thereby increasing **the**

22**solubility of the** analyte **in supercritical CO2**

, and the extraction proceeds more effectively [34]. The exponential curves were observed from all extracts suggest that Chrastil's model can be used to describe the SCE of SNL. Figure 4. Extraction yields of bioactive compounds from SNL berries

27**as a function of** CO2 **density and temperature** in terms **of**

(a) TPC, (b) TFC, and (c) TAC, and the corresponding Chrastil's model fits. Symbols represent experimental data. The yields of phenolics, flavonoids, and alkaloids were expressed as mg GAE/L CO2, mg QE/L CO2, and mg HE/L CO2, respectively. The parameter k in Chrastil's model

5**represents the number of** supercritical **CO2 molecules** involved **in the solvated complex**

according to the following equilibrium reaction: A + k CO2 ? A(CO2)k (9) In most cases, the constant k is not an integer because the formation of solvated complexes A(CO2)k is not always stable where some of the solvated compounds are less or more stable than others. As recorded in Table 3, the extracts (phenolic, flavonoid, and alkaloid) show a low k value. It indicates that only a slight amount of CO2 molecules is needed to form the solvated complexes; hence the extraction precedes effectively. Of the three extracts, phenolic (TPC) has the lower k value (2.137), which indicates that phenolic is extracted the most; this fact is consistent with the experimental result where extraction yield for phenolic (55.1677 mg/g) was the highest among the others. Alkaloid (TAC, k = 2.495) has a lower k value than that of flavonoid (TFC, k = 2.942); however, the extraction yield of the alkaloid (5.9460 mg/g) is lower than flavonoid (28.0308 mg/g). This deviation might arise due to alkaloid instability considering it has low thermal stability and tends to react with CO2 to form carbonate salt [27, 51]. Table 3. Fitted parameters of Chrastil's equation. Parameters k α β R2 [a]RD Phenolic – TPC 2.137 -10,080 20.13 0.9878 14.17 Flavonoid – TFC 2.942 -8,840 12.01 0.9871 17.95 Alkaloid – TAC 2.495 -9,378 12.11 0.9822 26.18 Parameter α obtained by non-linear least-squares fitting of experimental data are presented in Table 3 with TPC, TFC, and TAC values are 10080, 8840, and 9378, respectively. TPC has the highest absolute α values; means that the temperature highly influences the TPC yield. Furthermore, a temperature increase of twenty degrees gives rise in TPC, TFC, and TAC yields approximately 6.0, 4.3, and 2.6-fold, respectively. Again, there is a deviation for TAC, which is due to its instability in CO2. The negative value of α indicates an exothermic behavior of the supercritical extraction process. The parameter ? is associated with the

4**number and molecular weights of the solute and supercritical** fluid **based on the**

following equation: ? = ln(MA + kMCO2) + q – ln(kMCO2) (10) MA and MCO2 are the molecular weights of bioactive compounds and CO2, respectively, and q is a constant. Since the phenolics, flavonoids, and alkaloids were described as gallic acid, quercetin, and hyoscyamine equivalent; thus, the respective molecular weights are 170.12, 302.24, and 289.38 g mol-1. Accordingly, the constant q for the phenolic, flavonoid, and alkaloid can be calculated to be 19.10, 10.81, and 10.82. The objective function of

9**the average absolute relative deviation (ªRD) between experimental and calculated values** of **the** extraction yields **was** calculated by **the** following expression: **AARD** (%) = 100 ?**n** yexp,**i**

− ycalc,i n i=1 yexp,i (11) where yexp,i and ycalc,i are the experimental and calculated extraction yields for experimental point i, in the unit of g/L CO2,

12**respectively, and n is the** total **number of experimental points**

. All extraction yields have an R2 value close to 1, which indicates the apparent correlation between Chrastil's model to the resulting data. The R2 value could not depict the goodness of correlation for each extract individually. The goodness of data correlation can be covered by using the AARD value. Between the three extracts, an alkaloid (TAC) has the highest AARD; this indicates the big deviation of the experimental and calculated data. The high AARD for TAC is obviously due to its instability in CO2. 4. Conclusions Supercritical carbon dioxide extraction on Solanum nigrum has been successfully conducted. The bioactive compounds present in the extract were identified and quantified. The experimental designs have been performed using the Box-Behnken towards three parameters of temperature, time, and pressure. An empirical model, namely Chrastil's model, has been applied to correlate supercritical carbon dioxide's solubility as an extraction solvent with the extracted active compound. The Chrastil's adjustable parameters

4**k, α, and β are consistent with their physical meaning and**

comparable to other systems.

24**Funding This research received no external funding. Acknowledgments**

Financial support by the

4**National Taiwan University of Science and Technology**

through a joint research program with Widya Mandala Catholic University Surabaya is much appreciated.

20**Conflicts of Interest The authors declare no conflict of interest. References**

1. Campisi, A.; Acquaviva, R.; Raciti, G.; Duro, A.; Rizzo, M.; Santagati, N.A. Anti-oxidant Activities of Solanum nigrum L. Leaf Extracts Determined in In Vitro Cellular Models. Foods 2019, 8, https://doi.org/10.3390/foods8020063. 2. Knapp, S.; Barboza, G.E.; Bohs, L.; Särkinen, T. A revision of the Morelloid Clade of Solanum L. (Solanaceae) in North and Central America and the Caribbean. PhytoKeys

2019, 123, 1-144, https://doi.org/10.3897/phytokeys.123.31738 3. Dasgupta, N.; Muthukumar, S.P.; Murthy, P.S. Solanum nigrum Leaf: Natural Food Against Diabetes and its Bioactive Compounds. Res J Med Plant 2016, 10, 181-193, https://doi.org/10.3923/rjmp.2016.181.193. 4. Chen, Y.; Li, S.; Sun, F.; Han, H.; Zhang, X.; Fan, Y.; Tai, G.; Zhou, Y. In vivo antimalarial activities of glycoalkaloids isolated from Solanaceae plants. Pharm Biol 2010, 48, 1018-1024, https://doi.org/10.3109/13880200903440211. 5. Patel, A.; Biswas, S.; Shoja, M.H.; Ramalingayya, G.V.; Nandakumar, K. Protective Effects of Aqueous Extract of Solanum nigrum Linn. Leaves in Rat Models of Oral Mucositis. Sci World J 2014, 2014, https://doi.org/10.1155/2014/345939. 6. Wang, Y.; Xiang, L.; Yi, X.; He, X. Potential Anti-inflammatory Steroidal Saponins from the Berries of Solanum nigrum L. (European Black Nightshade). J Agric Food Chem 2017, 65, 4262-4272, https://doi.org/10.1021/acs.jafc.7b00985. 7. Umamageswari, M.S.; Karthikeyan, T.M.; Maniyar, Y.A. Anti-diabetic Activity of Aqueous Extract of Solanum nigrum Linn Berries in Alloxan Induced Diabetic Wistar Albino Rats. J Clin Diagn Res 2017, 11, FC16-FC19, https://dx.doi.org/10.7860/JCDR/2017/26563.10312. 8. Uwineza, P.A.; Waśkiewicz, A. Recent Advances in Supercritical Fluid Extraction of Natural Bioactive Compounds from Natural Plant Materials. Molecules 2020, 25, https://doi.org/10.3390/molecules25173847. 9. Danilović, B.; Đorđević, N.; Milićević, B.; Šojić, B.; Pavlić, B.; Tomović, V.; Savić, D. Application of sage herbal dust essential oils and supercritical fluid extract for the growth control of Escherichia coli in minced pork during storage. LWT 2021, 141, https://doi.org/10.1016/j.lwt.2021.110935. 10. Ahmad, T.; Masoodi, F.A.; Rather, S.A.; Wani, S.M.; Gull, A. Supercritical Fluid Extraction: A Review. J Biol Chem Chron 2019, 5, 114-112, https://doi.org/10.33980/jbcc.2019.v05i01.019. 11. Arnáiz, E.; Bernal, J.; Martín, M.T.; Diego, J.C.; Bernal, J.L.; Recio, L.T. Optimisation of the supercritical fluid extraction of anti-oxidants from broccoli leaves. Food Anal Method 2016, 9, 2174-2181, https://doi.org/10.1007/s12161-016-0399-4. 12. Cavalcanti, R.N.; Helmut, J.; Navarro, D.; Santos, D.T.; Rostagno, M.A.; Meireless, M.A.A. Supercritical Carbon Dioxide Extraction of Polyphenols from Pomegranate (Punica granatum L.) Leaves: Chemical Composition Economic Evaluation and Chemometric Approach. J Food Res 2012, 1, 282-294, https://doi.org/10.5539/jfr.v1n3p282. 13. Friedman, M.; Lee, K.R.; Kim, H.J.; Lee, I.S.; Kozukue, N. Anticarcinogenic Effects of Glycoalkaloids from Potatoes against Human Cervical, Liver, Lymphoma, and Stomach Cancer Cells. J Agric Food Chem 2005, 53, 6162-6169, https://doi.org/10.1021/jf050620p. https://biointerfaceresearch.com/ 14. Dafni, A.; Yaniv, Z. Solanaceae as Medicinal Plants in Israel. J Ethnopharmacol 1994, 44, 11-18, https://doi.org/10.1016/0378-8741(94)90093-0. 15. Do, Q.D.; Angkawijaya, A.E.; Nguyen, P.L.T.; Huynh, L.H.; Soetaredjo, F.E.; Ismadji, S.; Ju, Y.H. Effect of extraction solvent on total phenol content, total flavonoid content, and anti-oxidant activity of Limnophila aromatica. J Food Drug Anal 2014, 22, 296-302, https://doi.org/10.1016/j.jfda.2013.11.001. 16. Garmus, T.T.; Paviani, L.C.; Queiroga, C.L.; Cabral, F.A. Extraction of phenolic compounds from pepper- rosmarin (Lippia sidoides Cham.) leaves by sequential extraction in fixed bed extractor using supercritical CO2, ethanol and water as solvents. J Supercrit Fluid 2015, 99, 68-75, https://doi.org/10.1016/j.supflu.2015.01.016. 17. Goyeneche, R.; Fanovich, A.; Rodrigues, C.R.; Nicolao, M.C.; Scala, K.D. Supercritical CO2 extraction of bioactive compounds from radish leaves: Yield, anti-oxidant capacity and cytotoxicity. J Supercrit Fluid 2018, 135, 78-83, https://doi.org/10.1016/j.supflu.2018.01.004. 18. Harikrishnan, R.; Balasundaram, C.; Jawahai, S.; Heo, M.S. Solanum nigrum enhancement of the immune response and disease resistance of tiger shrimp. Penaeus monodon against Vibrio harveyi, J Aquac 2011, 318, 67-73, https://doi.org/10.1016/j.aquaculture.2011.05.024. 19. Pieczykolan, A.; Pietrzak, W.; Rój, E.; Nowak, R. Effects of Supercritical Carbon Dioxide Extraction (SC- CO2) on the content of tiliroside in the extracts from Tilia L. flowers. Open Chem 2019, 17, 302-312, https://doi.org/10.1515/chem-2019-0040. 20. Pilařová, V.; Hamimi, S.A.; Cunico, L.P.; Nováková, L.; Turner, C. Extending the design space in solvent extraction – from supercritical fluids to pressurized liquids using carbon dioxide, ethanol, ethyl lactate, and water in a wide range of proportions. Green Chem 2019, 21, 5427-5436, https://doi.org/10.1039/C9GC02140J. 21. Habila, J.D.; Bello, I.A.; Dzikwi, A.A.; Musa, H.; Abubakar, N. Total phenolic and anti-oxidant activity of Tridax procumbens Linn. Afr J Pharm Pharmacol 2010, 4, 123-128. 22. Molina-Cortés, A.; Sánchez-Motta, T.; Tobar-Tosse, F.; Quimbaya, M. Spectrophotometric Estimation of Total Phenolic Content and Anti-oxidant Capacity of Molasses and Vinasses Generated from the Sugarcane Industry. Waste Biomass Valori 2020, 11, 3453-3463, https://doi.org/10.1007/s12649-019-00690-1. 23. Woisky, R.; Salatino, A. Analysis of

propolis: some paramater and procedures for chemical quality control. J Apic Res 1998, 37, 99-105, https://doi.org/10.1080/00218839.1998.11100961. 24. Shi, P.; Du, W.; Wang, Y.; Teng, X.; Chen, X.; Ye, L. Total phenolic, flavonoid content, and anti-oxidant activity of bulbs, leaves, and flowers made from Eleutherine bulbosa (Mill.) Urb. Food Sci Nutr 2019, 7, 148-154, https://doi.org/10.1002/fsn3.834. 25. Aryal, S.; Baniya, M.K.; Danekhu, K.; Kunwar, P.; Gurung, R.; Koirala, N. Total Phenolic Content, Flavonoid Content and Anti-oxidant Potential of Wild Vegetables from Western Nepal. Plants 2019, 8, https://doi.org/10.3390/plants8040096. 26. Murga, R.; Sanz, M.T.; Beltran, S.; Cabezas, J.L. Solubility of three hydroxycinnamic acids in supercritical carbon dioxide. J Supercrit Fluid 2003, 27, 239-245, https://doi.org/10.1016/S0896-8446(02)00265-6. 27. Skwierczynski, R.D. Analysis of Medicinals. 21 ed. Remington-The Science and Practice of Pharmacy, ed. Troy, D.B.; Beringer, P. Maryland: Lippincott Williams & Wilkins, 2006. 28. Zermane, A.; Larkeche, O.; Meniai, A.H.; Crampon, C.; Badens, E. Optimization of essential oil supercritical extraction from Algerian Myrtus communis L. leaves using response surface methodology. J Supercrit Fluid 2014, 85, 89-94, https://doi.org/10.1016/j.supflu.2013.11.002. 29. Berkani, M.; Kadmi, Y.; Bouchareb, M.K.; Bouhelassa, M.; Bouzaza, A. Combinatıon of a Box-Behnken design technique with response surface methodology for optimization of the photocatalytic mineralization of C.I. Basic Red 46 dye from aqueous solution. Arab J Chem 2020, 13, 8338-8346, https://doi.org/10.1016/j.arabjc.2020.05.013. 30. Ahmad, A.; Rehman, M.U.; Wali, A.F.; El-Serehy, H.A.; Al-Misned, F.A.; Maodaa, S.N.; Aljawdah, H.M.; Mir, T.M.; Ahmad, P. Box–Behnken Response Surface Design of Polysaccharide Extraction from Rhododendron arboreum and the Evaluation of Its Anti-oxidant Potential. Molecules 2020, 25, https://doi.org/10.3390/molecules25173835. 31. Ye, C.L.; Lai, Y.F. Supercritical CO2 extraction optimization of onion oil using response surface methodology. Chem Eng Technol 2012, 35, 646-652, https://doi.org/10.1002/ceat.201100217. 32. Álvarez, C.E.; Vardanega, R.; Salinas-Fuentes, F.; Ramírez, J.P.; Muñoz, W.B.; Jiménez-Rondón, D.; Meireles, M.A.A.; Mezquita, P.C.; Ruiz-Domínguez, M.C. Effect of CO2 Flow Rate on the Extraction of Astaxanthin and Fatty Acids from Haematococcus pluvialis Using Supercritical Fluid Technology. Molecules 2020, 25, https://doi.org/10.3390/molecules25246044. 33. Vardanega, R.; Nogueira, G.C.; Nascimento, C.D.O.; Faria-Machado, A.F.; Meireles, M.A.A. Selective extraction of bioactive compounds from annatto seeds by sequential supercritical CO2 process. J Supercrit Fluid 2019, 150, 122-127, https://doi.org/10.1016/j.supflu.2019.01.013. 34. Sanjaya, R.E.; Tedjo, Y.Y.; Kurniawan, A.; Ju, Y.-H.; Ayucitra, A.; Ismadji, S. Investigation on supercritical CO2 extraction of phenolic-phytochemicals from an epiphytic plant tuber (Myrmecodia pendans). J CO2 Util 2014, 6, 26-33, https://doi.org/10.1016/j.jcou.2014.03.001. 35. Kostrzewa, D.; Dobrzynska-Inger, A.; Turczyn, A. Experimental Data and Modelling of the Solubility of High-Carotenoid Paprika Extract in Supercritical Carbon Dioxide. Molecules 2019, 24, https://doi.org/10.3390/molecules24224174. 36. Montesantos, N.; Maschietti, M. Supercritical Carbon Dioxide Extraction of Lignocellulosic Bio-Oils: The Potential of Fuel Upgrading and Chemical Recovery. Energies 2020, 13, https://doi.org/10.3390/en13071600. 37. Manjare, S.D.; Dhingra, K. Supercritical fluids in separation and purification: A review. Materials Science for Energy Technologies 2019, 2, 463-484, https://doi.org/10.1016/j.mset.2019.04.005 38. Rad, H.B.; Sabet, J.K.; Varaminian, F. Study of solubility in supercritical fluids: Thermodynamic concepts and measurement methods - a review. Braz J Chem Eng 2020, 36, 1367-1392, https://dx.doi.org/10.1590/0104-6632.20190364s20170493. 39. Coimbra, P.; Blanco, M.R.; Silva, H.S.R.C.; Gil, M.H.; de-Sousa, H.C. Experimental determination and correlation of artemisinin’s solubility in supercritical carbon dioxide. J Chem Eng Data 2006, 51, 1097- 1104, https://doi.org/10.1021/je060015y. 40. Aydi, A.; Zibetti, A.W.; Al-Khazaal, A.Z.; Eladeb, A.; Adberraba, M.; Barth, D. Supercritical CO2 Extraction of Extracted Oil from Pistacia lentiscus L.: Mathematical Modeling, Economic Evaluation and Scale-Up. Molecules 2020, 25, https://doi.org/10.3390/molecules25010199. 41. Vatani, Z.; Bajgiran, S.R.; Amini, G.; Tayyebi, S. Solubility modeling of supercritical fluid extraction in a wide range compounds: comparison between fuzzy-genetic and new empirical models. Energ Source Part A 2020, 42, 365-374, https://doi.org/10.1080/15567036.2019.1587083. 42. Ortiz, F.J.G.; Kruse, A. The use of process simulation in supercritical fluids applications. React Chem Eng 2020, 5, 424-451, https://doi.org/10.1039/C9RE00465C. 43. Belghait, A.; Si-Moussa, C.; Laidi, M.; Hanini, S. Semi-empirical correlation of solid solute solubility in supercritical carbon dioxide: Comparative study and proposition of a novel density-based modelCorrélation semi-empirique de solubilité des solutés solides dans le dioxyde de

carbone supercritique: étude comparative et proposition d'un nouveau modèle basé sur la densité. CR Chim 2018, 21, 494-513, https://doi.org/10.1016/j.crci.2018.02.006. 44. Chrastil, J. Solubility of Solids and Liquids in Supercritical Gases. J Phys Chem 1982, 86, 3016-3021, https://doi.org/10.1021/j100212a041. 45. Gomez-Prieto, M.S.; Castillo, M.L.R.D.; Flores, G.; Santa-Maria, G.; Blanch, G.P. Application of Chrastil's model to the extraction in SC-CO2 of b-carotene and lutein in Mentha spicata L. J Supercrit Fluid 2007, 43, 32-36, https://doi.org/10.1016/j.supflu.2007.05.010. 46. Ongkasin, K.; Sauceau, M.; Masmoudi, Y.; Fages, J.; Badens, E. Solubility of cefuroxime axetil in supercritical CO2: measurement and modeling. J Supercrit Fluid 2019, 152, https://doi.org/10.1016/j.supflu.2019.03.010. 47. Murga, R.; Sanz, M.T.; Beltran, S.; Cabezas, J.L. Solubility of some phenolic compounds contained in grape seeds, in supercritical carbon dioxide. J Supercrit Fluid 2002, 23, 113-121, https://doi.org/10.1016/S0896- 8446(02)00033-5. 48. Murthy, T.P.K.; Manohar, B. Modelling solubility of phenolics of mango ginger extract in supercritical carbon dioxide using equation of state and empirical models. J Food Sci Technol 2015, 52, 5557-5567, https://doi.org/10.1007/s13197-014-1667-1. 49. Ollanketo, M.; Hartonen, I.; Riekkola, M.L.; Holm, Y.; Hiltunen, R. Supercritical carbon dioxide extraction of lycopene in tomato skins. Eur Food Res Technol 2001, 212, 561-565, https://doi.org/10.1007/s002170100298. 50. Rovetto, L.J.; Aleta, N.V. Supercritical carbon dioxide extraction of cannabinoids from Cannabis sativa L. J Supercrit Fluid 2017, 129, 16-27, https://doi.org/10.1016/j.supflu.2017.03.014. 51. Popl, M.; Fahnrich, J.; Tatar, C. Chromatographic Analysis of Alkaloids. Chromatographic Science Series. New York: Marcel Dekker, Inc. Volume 53, 1990.

3**https://doi.org/10.33263/BRIAC115**

.1350213515

3**https://doi.org/10.33263/BRIAC115**

.1350213515

3**https://doi.org/10.33263/BRIAC115**

.1350213515

3**https://doi.org/10.33263/BRIAC115**

.1350213515

3**https://doi.org/10.33263/BRIAC115**

.1350213515

3**https://doi.org/10.33263/BRIAC115**

.1350213515

3**https://doi.org/10.33263/BRIAC115**

.1350213515

3**https://doi.org/10.33263/BRIAC115**

.1350213515

3**https://doi.org/10.33263/BRIAC115**

.1350213515

3**https://doi.org/10.33263/BRIAC115**

.1350213515

.1350213515 https://doi.org/10.33263/BRIAC115.1350213515
https://doi.org/10.33263/BRIAC115.1350213515 https://biointerfaceresearch.com/ 13502
https://biointerfaceresearch.com/ 13503 https://biointerfaceresearch.com/ 13504
https://biointerfaceresearch.com/ 13505 https://biointerfaceresearch.com/ 13506
https://biointerfaceresearch.com/ 13507 https://biointerfaceresearch.com/ 13508
https://biointerfaceresearch.com/ 13509 https://biointerfaceresearch.com/ 13510
https://biointerfaceresearch.com/ 13511 https://biointerfaceresearch.com/ 13512 13513
https://biointerfaceresearch.com/ 13514 https://biointerfaceresearch.com/ 13515