Supercritical Carbon Dioxide Extraction of Malaysian Stingless Bees Propolis: Influence of Extraction Time, Co-modifier and Kinetic Modelling

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Abstract. In the present work, the influence of extraction time and co-modifier on the yield of two types of MSB propolis, hard and sticky, using supercritical carbon dioxide extraction technique were evaluated. Different pressure, CO₂ flowrate and co-modifier percentage was studied at constant 40°C. SCCO₂ extraction was carried out at high (25MPa, 5 ml min⁻¹ CO₂, 7% ethanol) and low (15MPa, 3 ml min⁻¹ CO₂, 3% ethanol) operating conditions for both hard and sticky MSB propolis. The result shows that 240 minutes was the best and efficient extraction time. Meanwhile, at high operating condition in SCCO₂ technique has increased extraction yield of 1.1608g and 0.5656g for both hard and sticky MSB propolis with the addition of co-modifier. Extraction yield without co-modifier addition was 0.3602g and 0.0542g for hard and sticky MSB propolis, respectively. Co-modifier addition to the process had increase the extraction yield as much as 10 folds higher for sticky MSB propolis whilst, 3 folds higher for hard MSB propolis. These findings show that SCCO₂ method propose a feasible technique for MSB propolis extraction as it only require short extraction time and complemented with co-modifier application. Brunner and Esquivel model were used to determine the kinetic behaviours in the extraction process. The maximum extraction rate found was 3x10⁻⁴ g sec⁻¹ from the fitting the kinetic models.

1. Introduction
Recently, propolis is one of the bee products which has gained attention of researchers and consumer worldwide due to its numerous health benefits. It is a resinous substance collected by bees from exudates of surrounding plants, mixed with their saliva and waxes, gathered to their hive to protect against contamination and invaders, to seal holes, and to maintain temperature inside the hives.

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This product consists of 50% of resins, 30% of waxes, 10% of essential oil, 5% of pollen and 5% of organic compound and minerals. Propolis has been reported to possess various therapeutic activities for instance antitumoral, antifungal, anticancer, anti-inflammatory, antiviral and antibacterial properties. For this reason, it has been widely used in pharmacological, food and beverages industry to enhance human health and prevent diseases such as cancer, heart disease, inflammation and diabetes [1].

Supercritical CO$_2$ extraction is a technique employing CO$_2$ at its supercritical condition, temperature of 31°C and pressure of 7.38MPa, as a solvent to isolate compounds in natural matrixes. CO$_2$ is recognized as green solvent due to its non-toxic, non-flammable, non-polluting properties and generally acknowledged safe by FDA and EFSA. Supercritical CO$_2$ is also interesting because of its easily tuneable solvent strength combined with its high diffusivity properties. In addition, analyte recovery in this process is very simple and able to provide solvent-free analytes due to another CO$_2$ advantage that is, it is in gaseous form at room temperature and pressure. This make SCCO$_2$ extraction is an easy operate process. The ability of SCCO$_2$ extraction that can be carried out at low temperatures using non-oxidant medium is important for food and natural products sample preparation, in which admit thermally liable and easily oxidized compounds to be extracted [2].

To our literature extend, SCCO$_2$ technology has mainly used in application of sample preparation technique for the analysis of target compounds from foods and natural product. It has also commonly used in process development area, in which to extract target (bioactive or valuable) compounds from different sample matrices. SCCO$_2$ has been regarded as a promising tool not only from a laboratory point of view, but also for the industrial scale of food and natural products. For instance, there are several researches has been published in evaluation of the industrial economical practicability of some SCCO$_2$ developed processes, such as brewery spent grain management [3] and essential oil extraction from anise, fennel and rosemary [4]. On the other hand, there are wide studies of SCCO$_2$ application in laboratory scale such as extraction of Lamiaceae herbs [5], Strobilanthes crispus (Pecah Kaca) [6], aloe vera [7], chia seed oil [8], microalgae [9], Swietenia mahagoni seed [10], palm oil mesocarp [11] jatropha curcasl seed [12], piper betel linn leaves [13] castor oil [14] and many more.

In this study, influence of extraction time and co-modifier to extraction yield of two kinds Malaysian stingless bees propolis, hard and sticky propolis extracted using supercritical CO$_2$ technique were evaluated. One of crucial factors in SCCO$_2$ extraction process is the extraction time which explained by the time of SCCO$_2$ passes through extractor that can cause significant effects to the extraction yield. Extraction time is important to ensure adequacy of time and contact for extraction process to happen. Therefore, the extraction time is significant factor to obtain efficient process with maximum yield. Additionally, co-modifier addition to the SCCO$_2$ process is another influential factor that could increase the extraction yield by enhancing the SCCO$_2$ polarity to extract wider range of compounds. Ethanol is preferable as co-modifier in SCCO$_2$ process because it is safe and effective in assisting the extraction [15]. Lastly, the kinetic models of Brunner and Esquivel were employed to examine the extraction rate.

2. Methodology
2.1 Sample preparation
Hard & sticky propolis samples were supplied by Ecobee Shop Sdn. Bhd. from their farm located at Kulai, Johor, Malaysia. The samples were kept into freezer at -20°C overnight to freeze it and make it easy to further process. The samples were mashed into smaller size using pestle and mortar. After that, the samples were grounded and sieve into powder form with particle size of 300-500µm. Both samples were then stored in airtight container and kept in the freezer at -2°C until taken to further extraction process.

2.2 Propolis extraction
SCCO$_2$ extraction process was carried out using the instrument at Centre of Lipid Engineering and Applied Research (CLEAR), Universiti Teknologi Malaysia (UTM). Approximately 3g of raw hard or sticky propolis was weighed into a teabag and placed inside the extraction vessel. Function of the teabag is to prevent the sample particle from leaving the vessel. For start-up process, the circulating water bath was set at least 6°C first and the extraction chamber was set at 40°C. CO$_2$ was cooled and chilled prior to the experimental run in order to enable gas to be pumped for the rest of the experiments. The initial pressure of CO$_2$ must be in range of 6.2-6.8 MPa before starting the pump. The extraction vial was changed at every 20 minutes for 4 hours of extraction. After that the vial was dried in the oven to remove the ethanol modifier from the extract. Extraction yield for each experiment is expressed in gram (g) and calculated following equation below:

\[ \text{Extracted yield, g} = W_a - W_b \]

Where, $W_a$ is the weight of vial with extract after dry, g and $W_b$ is the weight of empty vial, g

2.3 Influence of extraction time to extraction yield
High operating condition (25MPa, 5ml min$^{-1}$ CO$_2$ flow rate, 7% EtOH) and low operating condition (15MPa, 3ml min$^{-1}$ CO$_2$ flow rate, 3% EtOH) was used to run both hard and sticky propolis SCCO$_2$ extraction in order to determine total extraction time. Extraction yield against time curve was plotted to choose the best extraction time. From the extraction curves, the equilibrium of diffusion region was selected as the best extraction time that explained the optimize condition for the extraction process. The extract sample was collected at interval of 20 minutes for 240 minutes, 4 hours.

2.4 Influence of co-modifier to extraction time
High operating condition (25MPa, 5ml min$^{-1}$ CO$_2$ flow rate, 7% EtOH) was used to run both hard and sticky propolis SCCO$_2$ extraction in order to determine presence of co-modifier. The SCCO$_2$ extraction was carried out with and without presence of co-modifier (EtOH) and compare the extraction yield obtained.

2.5 Kinetic Modelling
The extraction data graphs were fitted to the kinetic model. The first equation obtained from Esquivel model has one adjustable parameter presented as [16]:

\[ m_a = x_o m_b \left( \frac{t}{c t + t} \right) \quad (1) \]

Where $m_a$ is the mass of MSB propolis extracted (g), $x_o$ the mass of raw MSB propolis (g), $t$ is the extraction time (min), $m_b$ the percentage of MSB propolis extracted in the solute (%) and $c$ is an adjustable parameter (min). This equation was modified with the addition of one adjustable parameter [17] in the following the form:

\[ Y_t = Y_2 \left( \frac{t}{k_2 t + t} \right) \quad (2) \]

Where $Y_t$ is the total mass of extraction yield (g), $Y_2$ is the predicted total mass of extraction yield (g) and $k_2$ is the adjustable parameters (sec). The Brunner equation represents the empirical model and a specific solution of Fick’s law [18]:

\[ Y_t = E (1 - e^{-k_1 t}) \quad (3) \]

Where $Y_t$ is the extraction yield (%), $k_1$ is the rate constant (min$^{-1}$), $t$ is the extraction time (min) and $E$ is the percentage of MSB propolis extract in the solute (%) obtained by supercritical carbon dioxide extraction technique. This equation has one adjustable parameter (k) modified by adding one adjustable parameter in the following form [17]:

\[ Y_t = Y_2 (1 - e^{-k_1 t}) \quad (4) \]

Where $Y_t$ is the total mass of extraction yield (g), while $Y_2$ (g) is the predicted total mass of extraction yield and $k_1$ is the adjustable parameter (sec).

2.5.1 Calculation of Average Absolute Relative Deviation and Coefficient of Determination
The best suitable model is based on the average absolute relative deviation percentage (AARD %) between model and experimental. The equation is as follows:

\[
AARD \, (\%) = \frac{1}{n} \sum_{i=1}^{n} \left( \frac{Y_{\text{model}} - Y_{\text{exp}}}{Y_{\text{exp}}} \right) 
\]

where \( n \) is the number of data points, \( Y_{\text{model}} \) is the accumulation yield based on the model data, and \( Y_{\text{exp}} \) is the accumulation yield based on the experimental data.

Coefficient of determination will give the information on how good the model fitted with the experimental data. The equation of coefficient of determination as shown as Eq. (6).

\[
R^2 = 1 - \frac{\sum (y_i - f_i)^2}{\sum (y_i - \bar{y})^2} 
\]

Where \( \sum (y_i - f_i)^2 \) is the residual data as error of model correlated the experimental data and \( \sum (y_i - \bar{y})^2 \) is the variance of the data.

3. Result and Discussion

3.1. Influence of extraction time to extraction yield

Several factors must be taken into consideration prior to efficient supercritical carbon dioxide extraction. These include extraction conditions which are the pressure, temperature, flow rate, extraction time as well as the type of sample, method of sample preparation, type of fluid, modifiers and method of fluid feeding [19].

In order to determine total extraction time for SCCO\(_2\) extraction of hard and sticky propolis, the high operating condition, 25MPa, 5ml min\(^{-1}\) CO\(_2\) flow rate, 7% EtOH and low operating condition, 15MPa, 3ml min\(^{-1}\) CO\(_2\) flow rate, 3% EtOH was carried out for 240 minutes, 4 hours. Conventional propolis extraction was normally carried out for long hours of 6 to 8 hours. SCCO\(_2\) extraction is known to be rapid and efficient process, thus the process was reduced to only 4 hours and observing the extraction yield. SCCO\(_2\) extraction is found to require less extraction time as compared to other extraction process. For instance, SCCO\(_2\) extraction of lime needed only 30 minutes of extraction time compared to hydrodistillation process which needs 3 hours to obtain comparable oil yield results as per mentioned by Atti-Santos et al., [20]. Additionally, study by Guan et al., [21] demonstrate SCCO\(_2\) extraction of clove buds for only 2 hours resulted in higher oil yield which was 19.6% compared to extraction by steam distillation which resulted in 10.1% of oil yield after 8-10 hours.

As a result, extraction yield for both hard and sticky propolis at high and low operating condition were following extraction profile which consists 3 regions; constant extraction rate (CER), falling extraction rate (FER) and diffusion region (DIFF) throughout 4 hours of extraction time as per shown in Fig. 1 and 2. The trend showed in hard propolis SCCO\(_2\) extraction at high operating condition, 25MPa, 5ml min\(^{-1}\) CO\(_2\) flow rate, 7% EtOH, which the extraction yield had increased markedly for 140 minutes which called constant extraction rate, CER period and further increased slowly and tends to be saturated until 200 minutes which called falling extraction rate, FER period. Furthermore, the extraction yield reached maximum and become constant from 200 minutes to 240 minutes which the diffusion (DIFF) happened. Whilst, hard propolis SCCO\(_2\) extraction at low operating condition, 15MPa, 3ml min\(^{-1}\) CO\(_2\) flow rate, 3% EtOH had as well elucidated the same trend as per shown in Fig. 2. CER region happened initially for 120 minutes, continued to 180 minutes where FER region occurred and ended with diffusion phase until 240 minutes, 4 hrs of extraction time. This indicates 240 minutes; 4 hrs were adequate extraction time to reach the equilibrium state.
As mentioned by Yin et al., [22], these 3 regions composed in extraction process demonstrates rapid extraction of free solutes at constant extraction rate (CER), transitional stage of surface and internal diffusion of solvent and solute at falling extraction rate (FER) and slow extraction at diffusion region (DIFF) mainly due to only internal diffusion. During CER region, propolis extraction occurs rapidly and is dependent upon the solubility of the propolis solute in supercritical carbon dioxide fluids. The solubilized propolis solute is easily extracted until almost equilibrium condition controls the solute extraction into the supercritical carbon dioxide fluid. Following in FER region the propolis solute-matrix interaction must be disrupted hence cause a slower rate of extraction. At the same time, a transition to diffusion-controlled process also takes place in this region. Lastly DIFF region phenomenon is brought about either by the limited mobility of the propolis solute within the matrix, or by the limited access of supercritical carbon dioxide fluids to the target propolis solute. The propolis’s nature of complex matrix could also influence the extraction rate in this region. Complete extraction demonstrated in DIFF regions which equilibrium state achieved where there’s no more increasing of propolis solute extracted with a prolong extraction time [23].

This study results were comparable with study by De Zordi et al. [24], which mentioned that supercritical carbon dioxide extraction of Brazilian honeybees propolis resulted the highest extraction yield 14.3% at 45 ºC and 317 bar for 5 hrs extraction time. On the other hand, study by Paviani et al. [25] had reported that supercritical carbon dioxide extraction of ethanolic extract propolis needed 60 to 180 minutes of extraction time and showed no significant different after further increase the extraction time for more than 180 minutes.

3.2. Influence of co-modifier to extraction yield

The main disadvantages of SCCO₂ extraction process was the limitation of components that it can extract [26]. This is because of CO₂ non-polar properties, that restrain the ability of the solvent to extract polar solute which includes flavanols, flavonoids and tannins. Slight modification of the SCCO₂ polarity can be enhance by addition of co-modifier in the process to increase the ranges of extractable components.

Several bioactive compounds in propolis, such as flavonoids and cinnamic acid derivatives are categorized as a polar compound, hence they have minimal to zero solubility in SCCO₂. Therefore, incorporating a co-modifier in SCCO₂ extraction could help increase solubility strength between solvent and solute, thus improving the extraction efficiency. CO₂ alone and CO₂ with water were mentioned to be less effective for dissolving flavonoid compounds, whilst CO₂ with ethanol was observed as a more effective solvent [27].
Figure 3 shows that with addition of ethanol as modifier to the SCCO$_2$ extraction process has increased extraction yield of both hard and sticky propolis. For hard propolis, with addition of ethanol as modifier yielded in 1.1608g of extraction yield, whereas without addition of ethanol yielded in 0.3602g of extraction yield. It shows an increase as much three folds higher. Meanwhile, for sticky propolis, with addition of ethanol yielded in 0.5656g of extraction yield and without addition of ethanol yielded in 0.0542g of extraction yield. This shows huge increases as much as ten-fold higher.

![Figure 3: Extraction yield (%) of hard and sticky propolis extracted using SCCO$_2$ extraction with and without the presence of EtOH as modifier at high operating condition (25MPa, 5ml min$^{-1}$ CO$_2$ flow rate, 7% EtOH)](image)

Higher extraction yield was obtained from SCCO$_2$ extraction with addition of ethanol modifier than without addition of ethanol modifier for both hard and sticky propolis. This explained by addition of modifier in SCCO$_2$ extraction process could increase polarity of SCCO$_2$ and increase its solvent power. This provide more strength and solubility of SCCO$_2$ in extracting more compounds thus increase the extraction yield. Moreover, SCCO$_2$ is a non-polar and can only extract non-polar to slightly polar compounds. With addition of ethanol modifier, more polar compounds can be extracted during the extraction process. This result comparable with study by Ruslan et al. [15] which found addition of 5% methanol modifier to SCCO$_2$ extraction of betel nuts had enhance extraction yield and catechin concentration in the extract. Furthermore, Lee et al., [28] had used ethyl-acetate as a modifier in SCCO$_2$ extraction of Brazilian propolis and obtained an anti-cancer associated compound, 3,5-diprenyl-4-hydroxycinnamic acid, DHCA.

3.3. Kinetic Modelling

The mathematical models of supercritical carbon dioxide extraction provide a description of the extraction process. Furthermore, the results of mathematical modelling are typically used in the design, planning and scaling up of chemical processes from laboratory to industrial scale [29]. Numerous mathematical models provide descriptions of extraction processes, however, the most widely used are the empirical and kinetic models [30]. The empirical models evaluate the mass and heat transfer of extraction processes whereas kinetical models describe the differential mass balance before and after extraction [31, 32].
| Types of propolis | p (MPa) | CO₂ flowrate (ml min⁻¹) | Percentage of modifier (%) | Yield (g) | $y_2$ (g) | $k_2$ (sec⁻¹) | $y_2/k_2$ (g/sec⁻¹) | % Error | $R^2$ | Yield (g) | $1/k_1$ (1/sec⁻¹) | $y_2/k_1$ (g/sec⁻¹) | % Error | $R^2$ |
|------------------|--------|------------------------|---------------------------|----------|----------|-------------|-------------------|---------|--------|----------|-------------------|------------------|---------|--------|
| Sticky           | 25     | 5                      | 7%                        | 0.826    | 1.721    | 1559        | 1.1 E-4           | 3.07    | 0.999  | 1.058    | 1.02 E-4          | 1.07 E-4         | 2.42    | 0.999  |
| Sticky           | 15     | 3                      | 3%                        | 0.225    | 0.689    | 2983        | 2.3 E-5           | 1.47    | 0.999  | 0.444    | 4.92 E-5          | 2.18 E-5         | 6.66    | 0.999  |
| Hard             | 15     | 3                      | 3%                        | 0.442    | 1.093    | 9452        | 1.2 E-4           | 5.82    | 0.983  | 0.843    | 1.07 E-4          | 0.00024         | 9.47    | 0.982  |
| Hard             | 25     | 5                      | 7%                        | 0.075    | 2.889    | 1200        | 3 E-4             | 1.62    | 0.998  | 1.905    | 1.3 E-4           | 2.50 E-4         | 1.20    | 0.996  |
In this study there were two kinetic models; Esquivel and modified Brunner model for mathematical interpretation of MSB propolis, hard and sticky SCCO$_2$ extraction. The two adjustable parameters ($Y_2$ and $k_2$; $Y_1$ and $k_1$, respectively) were examined using the models. Based on average of coefficients of determination ($R^2$), the most suitable model was determined as presented in Tab. 1. The lowest average of coefficients of determination is the most suitable to fit mathematical model and experimental data.

| Model         | $\frac{Y_2}{k_2}$ (g/sec) | Error (%) | $R^2$  |
|---------------|-----------------------------|-----------|--------|
| Esquivel      | $1.298 \times 10^{-4}$      | 2.99      | 0.995  |
| Brunner       | $8.306 \times 10^{-5}$      | 4.94      | 0.995  |

Figure 4: Kinetic model fitted at high operating condition, 25MPa, 5ml min$^{-1}$ CO$_2$ flow rate, 7% EtOH a) Sticky Propolis  b) Hard Propolis

Figure 5: Kinetic model fitted at low operating condition, 15MPa, 3ml min$^{-1}$ CO$_2$ flow rate, 3% EtOH: a) Sticky Propolis  b) Hard Propolis
Table 2 shows that the Esquivel model shows slightly better fit between the calculated values and experimental data compared with Brunner model. The calculated extraction rate of the Esquivel model and yield of MSB propolis extract yield (response) was used for examination influence of operating condition, co-modifier and type propolis (hard and sticky propolis). The maximum calculated extraction rate (g sec$^{-1}$) and yield of propolis extract (g) were set to obtain the maximum yield extract. The highest extraction rate, 3x10$^{-4}$ g sec$^{-1}$ and yield of propolis extract, 2.889g were obtained from MSB hard propolis SCCO$_2$ extraction at high operating condition, 25MPa, 5ml min$^{-1}$ CO$_2$ flow rate, 7% EtOH. The lowest extraction rate, 2.3x10$^{-5}$ g sec$^{-1}$ and yield of propolis extract, 0.681g were resulted from MSB sticky propolis SCCO$_2$ extraction at low operating condition, 15MPa, 3ml min$^{-1}$ CO$_2$ flow rate, 3% EtOH. High operating condition yielded higher extraction rate and yield of propolis extract as compared to low operating condition. This could be explained that at high operating condition with higher pressure had increased the density and diffusivity of the supercritical carbon dioxide fluid hence enhance the solvation power of the fluid to extract more MSB propolis extract effectively [33]. Moreover, high operating condition with higher SCCO$_2$ fluid flow rate provide more frequent solute-solvent contact between MSB propolis analyte with SCCO$_2$ fluid thus allow more extraction process to happen and increase the extraction yield. This as well described by Bimakr et al., [34] that higher SCCO$_2$ flow rate of 9g min$^{-1}$ had resulted in higher extraction yield and concentration of catechin, epicatechin, rutin, luteolin, myricetin, apigenin and naringenin in spearmint SCCO$_2$ extraction as compared to lower SCCO$_2$ flow rate of 3g min$^{-1}$. Additionally, higher percentage of co-modifier used in high operating condition had enhanced the polarity of SCCO$_2$ to extract wider range of polar compound and raised the extraction yield. Similarly, uses of ethanol as co-modifier in SCCO$_2$ extraction of peanut skins had yielded better extract quantity and compositions as compared to without uses of co-modifier. SCCO$_2$ complemented with ethanol as co-modifier in the process helped to break the peanut skins matrix and extract more targeted compound inside the material [35].

4. Conclusion
In conclusion, 240 minutes, 4hrs of extraction time for MSB propolis SC-CO$_2$ extraction is adequate and efficient as it already reached diffusion region that indicated the maximum oil yield was extracted. Prolong extraction time is not economic efficient because of high amount of solvents, energy and cost consumption. Furthermore, MSB propolis SCCO$_2$ extraction only require shorter extraction time as compared to conventional Soxhlet extraction which normally require at least 6 hrs of extraction time. Meanwhile, addition of co-modifier to MSB propolis SCCO$_2$ extraction had also increase the extraction yield by enhancing the SCCO$_2$ polarity to extract more wider range of compound. Presence of co-modifier not only resulted in better yield; it has also provided higher chances of extracting more valuable polar compounds in the propolis sample. For kinetic modelling, the Esquivel model shows slightly better fit between the calculated values and experimental data compared with Brunner model. MSB hard propolis SCCO$_2$ extraction at high operating condition, 25MPa, 5ml min$^{-1}$ CO$_2$ flow rate, 7% EtOH had figured the highest extraction rate of 3x10$^{-4}$ g sec$^{-1}$ and yield of propolis extract of 2.889g.

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