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High Pressure CO_2-Assisted Extraction for Rapid Phenolic Isolation: A Brief on Recent Progress and Its Future Direction

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ABSTRACT
Phenolics are bioactive compounds produced in plants, which are primarily associated with plants defense mechanisms. The compounds possessed antioxidant and anti-inflammatory properties which exert favourable effects on human health. However in order to achieve the benefit, the phenolics need to be isolated from the plants via a suitable extraction process. Among the most recently studied technique is high pressure carbon dioxide-assisted extraction (HPCDAE). The technique involves pressurization and a rapid release of the carbon dioxide from the extraction system. Based on limited number of studies available, the HPCDAE shows promising prospect as an efficient and a rapid method for phenolics extraction. This review looks into the current progress of HPCDAE studies for phenolics, and compares its performance against other extraction techniques. Furthermore, its novelty and future directions are discussed toward the end of the review.

Keywords: *Green extraction, non-conventional extraction, high pressure CO2, bioactive compound, mass transfer kinetic, high-yield*

1. INTRODUCTION

Phenolics are secondary metabolites produced by plants, associated generally with plant's defense mechanisms against environmental stresses [1]. Extensive studies have shown that phenolics confer myriad health benefits on human, which are attributed to their antioxidant and the anti-inflammatory properties [2]. Phenolics compounds were proven to exert beneficial health effects and the efficacy to ameliorate diseases such hypertension [3] and cancer [4]. Extraction is a process by which bioactive compounds located in the plant matrix are separated and transferred into a suitable solvent [5]. Conventional methods of extraction such as percolation, maceration and Soxhlet had been utilized to extract the bioactive compounds. Unfortunately, there are many drawbacks associated with these conventional methods. The most notables are the high-energy consumption and the prolonged process [6]. These undesirable characteristics have prompted researchers to look for better extraction process. In recent years, many new non-conventional extraction methods have been explored; among them are the pressurized liquid extraction (PLE) [7], supercritical fluid extraction (SFE) [8], and high pressure CO_2-assisted extraction (HPCDAE) [9–11]. HPCDAE in particular, has been shown to extract phenolics with high yield and with shorter extraction period. During the HPCDAE process, sample of plant is placed in an extraction vessel and mixed with a suitable solvent of choice [10]. Temperature of the extraction vessel is normally set above the critical temperature of CO_2. Then, the CO_2 is pumped into the vessel until the desired pressure is reached. The extraction process is allowed to take place at the desired pressure and temperature for a determined period. Finally, the CO_2 is released rapidly from the system. The extract is collected from the extraction vessel, and may require a further filtration process in order to obtain a pure final extract.

To date, no work has been done to review the studies related to HPCDAE. In this review, the process and the progress of HPCDAE on phenolics extraction, in particular the extraction parameters along with their effects are scrutinized for the first time. Efficiency and novelty of the technique in light of other techniques are discussed. Finally, this review is concluded by presenting the future directions for the HPCDAE study.

2. HISTORY OF HPCDAE

Since the 1980s, high pressure CO_2 has been used extensively as a non-thermal food preserving technique. CO_2 is used widely in many food related applications due to several advantages; it is known to be inert, non-toxic, inexpensive, and belongs to the Generally Regarded as Safe (GRAS) group [12]. Food preservation is achieved through deactivation of detrimental microorganisms [13,14] and degrading enzymes [15,16]. The deactivation is achieved through structural changes afflicted onto the microorganisms and the enzymes when the CO_2 undergoes rapid depressurization from the food sample. The utilization of high pressure CO_2 for plant extraction had only begun in the late 2000s. One of the pioneering work reported is the extraction of oil from the canola flakes [17]. Meanwhile, extraction of phenolics was first performed on red cabbage (*Brassica oleracea L. var. capitata f. rubra*) for the isolation of anthocyanins [10]. Unfortunately, only several additional studies have been conducted for phenolics extraction. To date, HPCDAE have been used for phenolics extraction from the jabuticaba (*Myrciaria cauliflora*) skins [9] and the strawberry-tree (*Arbutus unedo*) fruits [11]. This lack of study leads to a significant gap of knowledge in regards to HPCDAE which requires more research in the future.

3. HPCDAE SETUP

A simplified diagram of the HPCDAE system setup is shown in Figure 1. The setup is based on the study done by Xu et.al (2010). The overall extraction process consists of several steps. First, the extraction vessel which houses the sample is pressurized with CO_2, during which the release valve is kept closed. The CO_2 flows through a cooling unit before it is pumped into the extraction vessel until the desired pressure is attained. The temperature of the extraction vessel is controlled by a heating bath. Next, the extraction process is allowed to occur for a designated period at the determined pressure and temperature. Finally, after the desired time of extraction is reached, the extraction vessel is rapidly depressurized by opening the release valve. Apart from the above mentioned system setup, the study done on jabuticaba skins integrates a back-pressure regulator that controls the pressure level [9]. However the addition of the regulator may be redundant and costly, since the overall process is done in a static mode. Moreover, the total time taken for the extraction is short, which is less than 30 minutes.

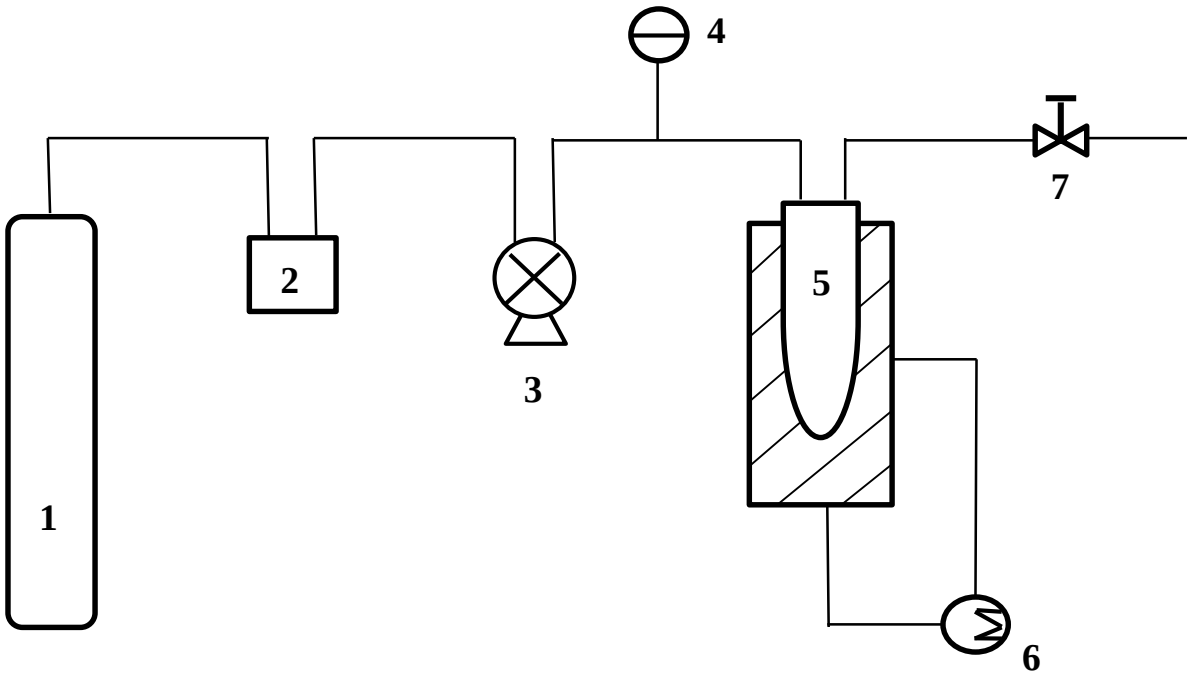

Figure 1 Diagram of High Pressure Carbon Dioxide-Assisted Extraction (HPCDAE) system. 1 CO_2 cylinder; 2 Cooling unit; 3 Pump; 4 Pressure transducer; 5 High pressure vessel; 6 Heating bath; 7 Release valve

4. HPCDAE PARAMETERS

Extraction parameters studied are summarized in Table 1. The parameters were based on the three studies done so far and are organized in a year-of-study sequential manner in order to illustrate the progress made in HPCDAE. Table 1 shows the HPCDAE parameters. In total six parameters are included and their effects on extraction are discussed critically in the following sections.

4.1 Ratio of solid:liquid (RS:L)

The solid to liquid ratio ($R_{S:L}$) is determined based on the volume of solid sample compared to the volume of solvent (volume/volume). In the first two studies, the $R_{S:L}$ was fixed at 1:10 [9,10]. Only in the study involving strawberry-tree, three different $R_{S:L}$ were tested; 1:10, 1:20, and 1:30 [11]. Between the three $R_{S:L,}$ the highest total phenolics content (TPC) value was achieved when the $R_{S:L}$ is greatest (i.e. $R_{S:L}$ of 1:30). The outcome can be explained through the greater amount of solvent that was used. The higher volume of solvent present in the 1:30, as compared to the other ratios enables greater amount of solute from the sample to dissolve. However, the $R_{S:L}$ ratio was determined through a conventional solid-liquid extractions which were done under the atmospheric pressure and at the room temperature. Therefore, it is necessary to conduct the study of the $R_{S:L}$ parameter via HPCDAE in order to determine its real effect on extraction.

4.2 Ratio of solid and liquid: CO_2 ($R(S\text{-}L/CO_2)$)

The ratio of solid and liquid against the CO_2 is a parameter that is unique to the HPCDAE. It is based on the volume of the extraction vessel occupied by the sample and solvent, against the remaining volume. For instance, an extraction done in a 500 ml vessel at $R_{(S\text{-}L/CO2)}$ of 20% would means that the sample and solvent will occupy 100 ml of the total volume. High density CO_2 is considered to fill the rest of the empty vessel during the extraction. Initially the $R_{(S\text{-}L/CO2)}$ was represented by numerical unit; however percentage unit was used in the latter studies. In the red cabbage extraction study, the total anthocyanins content (TAC) increases as the $R_{(S\text{-}L/CO2)}$ gets smaller (i.e., the volume of high density CO_2 is greater) [10]. A similar pattern was also observed in the study involving jabuticaba skins for both its TAC and TPC values [9], and for the TPC value in the extraction of strawberry-tree fruits [11].
As mentioned earlier, the rapid release of CO_2 from the extraction vessel causes destruction of cellular structural integrity. When the $R_{(S\text{-}L/CO2)}$ decreases, the volume of high density CO_2 in the extraction vessel becomes greater. This enhances the explosive effect which occur during the depressurization, which in turns amplified the destruction of the cell structures [10]. As a consequence, the mass transfer of solutes from the inner cells into the solvent is enhanced and therefore expediting and improving the extraction process.

4.3 Temperature and pressure

Temperature and pressure are factors that affect extraction. In every study involving HPCDAE, higher extraction yield was achieved when the pressure and the temperature of the process were higher. At high pressure the density of CO_2 increases, which in turn increases its solvating power. High pressure also causes rupturing of the plant cells, allowing bioactive compounds which are located inside the cell to release into the surrounding, making them more accessible for binding with the solvent [18]. Meanwhile, high temperature reduces the viscosity of the solvent, which promotes higher diffusion of solutes from the sample matrix into the solvent. Moreover, higher temperature enhances the breaking of covalent bonds that bind the bioactive compounds to the plant matrix, results in a greater thermal desorption of compounds into the surrounding [19]. Under excessive heat, plant's cell wall is severely impaired allowing easier and greater solvent penetration into the cells. Once inside the cells, the solvent can bind more readily with the bioactive compounds. Another positive effect of high temperature on extraction is achieved through elevation of solute's vapor pressure which causes the solute to be more soluble with the solvent. Despite the positive effects associated with HPCDAE done at high pressure and high temperature, a reverse pattern has also been reported. A negative effect was reported on the TAC value during the jabuticaba skins extraction, over a continual and simultaneous elevation of the temperature and the pressure [9]. It is postulated that the anthocyanins molecules degrade under the high temperature and pressure.

4.4 Sample particle size

Specific mention of the sample particle size used in the extraction process was reported solely in the study involving strawberry-tree fruits. However only one particle size was chosen, which is between 0.707 – 1.000 mm [11]. By looking into studies involving phenolics extraction via the SFE method, it is evident that the sample particle size can significantly affect the outcome. Sample with smaller particle size has larger mass transfer areas, which allows more interaction between the solutes and the solvents and thus increases the extraction [20]. However, if the sample size becomes too small, detrimental effect on the extraction process arises. The small sample particles experiences intense compaction under the high pressure condition, creating a highly dense sample bed which consequently increases the mass transfer resistance [21]. Furthermore, channeling inside the sample bed can occurs, which causes inhomogeneous distribution of the solvent. Therefore, based on the findings from the supercritical CO_2 method, the effect of sample particle size can be included as part of the parameters in the future study of HPCDAE.

4.5 Solvent

The effect of solvent on the extraction was observed in the study involving strawberry-tree fruits [11]. Water, ethanol, and combination of both solutions at various ratios were utilized, resulting in different TPC values with no particular pattern. The observations are due to differential selectivity and affinity of the various solvent solutions towards specific compounds in the strawberry-tree fruit sample. A study done by Jacotet-Navarro et. al (2018) on rosemary extract has shown that the highest yields of two different phenolic compounds; rosmarinic acid and carnosic acid, were achieved at different ethanol solvent concentrations. Rosmarinic acid was best extracted at 30% ethanol concentration, while for the carnosic acid it was the 70% ethanol. Similar outcomes were also reported on the study done for phenolics extraction from ligno-cellulosic sub-products [23]. However the study on the effect of the solvents in the strawberry-tree study was done through a conventional solid-liquid extraction technique and not through HPCDAE. Therefore in the future, the investigation can be conducted under high pressure CO_2 to determine the real effect of solvents on the extraction process.

5. KINETIC OF EXTRACTION

Kinetic data is imperative for understanding the extraction process and for future up-scaling. Kinetic study involves studying the rate of movement of solute from inside the cells into the extracellular environment, which can be represented by certain mathematical modeling [10]. When solutes move from inside the cell, they encounter mass transfer resistances from several organelles and cellular structures such as the cell vacuole, cell membrane and cell wall. However in studying the kinetic of extraction, only the cell wall's resistance is taken into account while the resistances from other sources are considered negligible.

For HPCDAE, the extraction kinetic modeling study was performed by Xu et al. using two well established kinetic models (2010). Kinetic models used are the general mass transfer and the Fick's second law of diffusion. Values of the extraction yields were fitted into the two models, and it was concluded that the data is better fitted into the general mass transfer model, with a more significant regression coefficient ($R^2 > 0.97$). The general mass transfer kinetic model consists of two phases; a fast recovery phase and a steady state phase. In the first phase, solutes are rapidly transferred into the solvent, while in the second phase the solute's transfer has reached a plateau with only minimal movement of solutes takes place. The study done gives an early indication on the kinetic of HPCDAE. However, more studies are required in order to fully understand the underlying kinetic extraction mechanism.

Table 1
HPCDAE parameters of solid:liquid ratio ($R_{S/L}$), ratio of solid and liquid:CO_2 ($R_{(S+L/CO2)}$), temperatures, pressures, sample sizes and solvents

Sample	$R_{S/L}$	$R_{(S-L/CO2)}$	Temperature (ºC)	Pressure (bar)	Size	Solvent	Ref.
Red cabbage	1:10	140/710 ml/ml 410/440 ml/ml 690/160 ml/ml	40 60	100	Not stated	Acidified water	[10]
Jabuticaba skins	1:10	20% 50% 80%	40 60 80	65 100 135	Not stated	Acidified water	[9]
Strawberry-tree fruits	1:10 1:20 1:30	20% 50% 80%	40 55 70	100 175 250	0.707 – 1.000 mm	Water Ethanol 25% Ethanol 50% Ethanol 75% Ethanol 100%	[11]

6. HPCDAE PERFORMANCE

Efficacy of HPCDAE against conventional and other non-conventional techniques is evaluated based on two criteria; the phenolics yields and the extraction time. The summary of the HPCDAE efficiency compared to the other techniques is shown in Table 2. In general, the HPCDAE for all three studies show that the technique resulted in phenolics yields that are comparable to other techniques. Moreover, except for the PLE, HPCDAE has the shortest extraction period. This property of expedited process is advantageous for up-scale and commercial production process. Even though the HPCDAE requires more time than the PLE, it is superior in terms of cost, because the latter requires specialized devices that are associated with

high initial investment cost [24]. It has been established that phenolics content of plants originating from different geographical locations and climates can vary significantly [25,26]. Therefore the study on jabuticaba skins offers the best insights into the HPCDAE performance since all of the samples originated from the region of São Paulo, Brazil. In terms of the extraction brevity, the HPCDAE was second only to PLE. However, it has the lowest TAC when compared to the other techniques. This outcome can be attributed to two factors. First is the use of a different solvent; acidified water in the HPCDAE as compared to ethanol for the other methods. The second reason, as pointed out by the author, is the drying process done on the HPCDAE sample which has caused significant degradation of the anthocyanins [9]. Based on the vis-à-vis comparison, it is apparent that HPCDAE has the potential to be utilised as a rapid and efficient extraction technique.

7. NOVELTY OF HPCDAE

HPCDAE is a recent technique utilized for extraction of bioactive compounds. Although it shares some similarity with other more established non-conventional techniques, especially the PLE and the SFE, HPCDAE exhibits several characteristics and advantages which establishes its novelty. The main attribute that sets the HPCDAE apart from the PLE and SFE is the rapid decompression of CO_2 from the extraction chamber, which is absent in the last two. When CO_2 is rapidly released, explosive effect is triggered which destroys the plant cells. Furthermore, it causes structural distortion and rupturing of degradative enzymes and microorganisms that are present in the sample. This event stops the degradation of the bioactive compounds and prolongs the shelf life and preserves the efficacy. Furthermore, pressurized CO_2 alters the solvent property which enhances its ability for better extraction.

The PLE operates based on the principle of elevated extraction pressure and temperature. The high pressure enables the liquid to stay in a liquid state despite the high temperature applied. It also forces the solvent to diffuse into the solid matrix. Meanwhile higher temperature favors the extraction by enhancing the diffusivity of solvent through reduction of its viscosity and surface tension [27]. Both the elevated pressure and temperature alter the characteristics of solvent used, making the solvent more effective for extraction. Meanwhile in HPCDAE along with the higher pressure and temperature applied, alteration of solvent is further influenced by the addition of pressurized CO_2. In validating the effect of pressurized CO_2 on modifying the solvent, three sets of run at optimum conditions identified by a Response Surface Methodology (RSM) were done via HPCDAE, control HPCDAE, and PLE [9]. The optimum conditions identified are temperature of 80^{o}C and pressure of 117 bar (except for the control; at atmospheric pressure). The readings of TAC were recorded every 5 minutes throughout the process and were taken for 45 minutes. HPCDAE registered the highest TAC values, followed by the control HPCDAE experiment and the PLE; at 20 minutes the values are 2.2 mg of Cy-3-glucoside/g dry material, 1.6 and 0.58 respectively. The control experiment which didn't utilize pressurized CO_2 registered a 3-fold increment against PLE. The low amount of anthocyanins in PLE can be attributed to degradation of the compounds under intense pressure and temperature. Addition of pressurized CO_2 in the HPCDAE further increased the amount of extracted anthocyanins, which substantiates the hypothesis of enhanced solvent modification by the CO_2. Apart from the enhanced solvent modification, HPCDAE possesses another advantage over the PLE since it doesn't require additional purging with inert gas; a practice which is common in the PLE to minimize sample losses or to avoid the memory effect [27]. HPCDAE is very similar to SFE; both utilized CO_2 at sub-critical or supercritical state, and they involved addition of organic co-solvent for polar compounds extraction. In fact the HPCDAE of the strawberry-tree fruits was done using a supercritical fluid extractor. Despite the similarity, HPCDAE possesses advantageous and overcomes several drawbacks associataed with SFE. By utilizing the simpler HPCDAE setup as shown in Figure 1, the system overcomes high setup cost associated with SFE, which as a result would reduce the overall cost of manufacturing [28]. Conventional SFE faces limitation on applicable sample size; too small particles can cause clogging in the tubing and connections [29]. Particle size has a direct effect on the extraction yield. Smaller particle has larger mass transfer area and less structural hindrance which results in better contact of bioactive compound with the solvent. Another drawback of SFE is the disability to utilize a fresh sample. The use of fresh sample is more preferable than dried since the latter has been associated with lower extraction yield [9]. However, utilization of sample with high moisture content is not preferred with SFE since co-extraction with water can cause the formation of ice-blocking inside the components and parts especially the separator container [21].

SFE is known for its selectivity, which is made possible through manipulation of the extraction parameters, in particular the temperature, pressure and co-solvent concentration. However based on the study done on the strawberry-tree fruits, selective extraction has been established with the HPCDAE. The authors concluded that

Table 2
HPCDAE performance against other non-conventional techniques in terms of anthocyanins yield and extraction time

Sample	Sample origin	Technique	Time	Total anthocyanins content	Parameters / conditions		Ref.
Red cabbage	China	HPCDAE	13 minutes	583 µg/g	Temperature Pressure R $_{(S\text{-}L/CO_2)}$ $R_{S/L}$ Solvent	60 ^{O}C 100 bar 140 ml / 710 ml 1:10 Acidified water	[11]
		Aqueous extraction	27 minutes	556 µg/g	Temperature Solvent	60 ºC Acidified water	
	Iran	Ultrasound assisted	30 minutes	930 µg/g	Output power Temperature Solvent	100W 15 ºC Distilled water	[36]
	Italy	Pressurized liquid extraction	7 minutes	662 µg/g	Temperature Pressure Solvent	99 ºC 50 bar Water + 5% ethanol + formic acid	[37]
	Turkey	Ultrasound assisted	75 minutes	170 µg/g	Temperature Solvent Sample : solvent ratio	40 ºC 43% ethanol 1:3 (w/v)	[38]
Jabuticaba skin	Brazil	HPCDAE	20 minutes	2.2 mg/g	Temperature Pressure R $_{(S\text{-}L/CO_2)}$ $R_{S/L}$ Solvent	80 ºC 117 bar 20% 1:10 Acidified water	[9]
		Pressurized liquid extraction	20 minutes	0.58 mg/g	Temperature Pressure Solvent	80ºC 117 bar Acidified water	
	Brazil	Pressurized liquid extraction	9 minutes	2.5 mg/g	Solvent Temperature Pressure	Ethanol 80 ºC 50 bar	[39]
	Brazil	Ultrasound assisted	120 minutes	4.8 mg/g	Output power Temperature Solvent	81 W Room temperature Ethanol 99.5%	[40]
		Agitated bed extraction	120 minutes	6.2 mg/g	Temperature Agitation Solvent	30 ºC 150 rpm Ethanol 99.5%	
		Ultrasound assisted & agitated bed extraction	10 minutes (UA) + 120 minutes	5.2 mg/g	Output power Temperature Agitation Solvent	81 W 30 ºC 150 rpm Ethanol 99.5%	
		Soxhlet	8 hours	5.0 mg/g 5.2 mg/g	Solvent Solvent	Ethanol 99.5% Ethanol 99.5% pH3	
	Brazil	Ultrasound assisted	50 minutes	6.0 mg/g	Output power Temperature Solvent	150 W 30 ºC Acidified ethanol 46%	[41]

Table 2 (continued)

Sample	Sample origin	Technique	Time	Total phenolics content	Parameters / conditions		Ref.
Strawberry -tree fruit	Portugal	HPCDAE	15 minutes	37 mg GAE / g d.w.	Temperature Pressure R (S-L/CO_2) $R_{S/L}$ Solvent	70 ^{O}C 250 bar 20% 1:20 Ethanol 50%	[11]
	Spain	Aqueous extraction	30 minutes	19.7 mg GAE / g d.w.	Solvent	Methanol Acetone	[42]
	Portugal	Aqueous extraction	12 hours	126.8 mg GAE / g d.w.	Solvent	Methanol	[43]
	Turkey	Aqueous extraction	1 hour	10.7 mg GAE / g d.w.	Solvent	Petroleum ether	[44]

there is a strong correlation between the increasing antioxidant activities of oxygen radical absorbance capacity (ORAC) with the increased of galloyl hexoside and 5-O-galloylquinic acid contents. Selectivity in HPCDAE can be attributed to the common extraction parameters that it shares with SFE. Besides temperature and pressure, the $R_{S-L/CO2}$ parameter in HPCDAE is quite similar to the extraction parameter of co-solvent concentration in SFE. The amount of liquid solvent presents in the HPCDAE determines the volume of CO_2 that exists in the pressurized vapor state; similarly the predetermined concentration of co-solvent in SFE also set the same limitation towards pressurized CO_2. Through manipulation of all three parameters, selectivity can be established in both the HPCDAE and SFE.

8. FUTURE RESEARCH DIRECTIONS

To date only three studies have been performed on HPCDAE. By looking into these studies, enhancement on the understanding of the HPCDAE can be made by modifying and improving some parts of the experimental design.

a. Only the study on strawberry-tree dwelled into the effect of solid: liquid ratio ($R_{S:L}$). However it was done via a conventional solid-liquid extraction process. Therefore the study on the effect of $R_{S:L}$ can be done in a pressurized condition and elevated temperature to reflect the real extraction conditions under HPCDAE.

b. Effects of the samples particle size on the extraction performance.

c. Effects of different solvents under HPCDAE conditions. Selectivity of solvents towards specific ompounds can be analysed via the chromatography techniques.

Apart from the existing parameters, additional parameters can be included in order to enhance the understanding of the HPCDAE.

a. Effect of water content (moisture) in the sample. Moisture has been shown to influence the extraction outcome. In a study conducted to extract phenolics from rehydrated olive paste, the moisture content of the samples exerted significant influence on the final TPC [30].

b. Rate of depressurization. It has been established that the rapid release of CO_2 creates an explosive effect that causes structural breakdown of the cells. Despite this property which favors the extraction, the explosive effect is also attributed to the destruction of degrading enzymes during food pasteurization process. Therefore, there exists a possibility that the CO_2 explosion may compromise the integrity of the phenolics structures and thus their functions. The depressurization rate can be studied in order to determine an optimize level that balance both of the parallel effects.

c. Imaging studies of the cell structure prior to and after the CO_2 depressurization to visualize the explosive effect. Imaging equipment such as the scanning electron microscope (SEM) [31] and the transmission electron microscope (TEM) [32] can be utilized for this purpose.

d. Comparative study to measure the effectiveness of the HPCDAE, against other non- conventional techniques for phenolics extraction that have not been reported so far, such as the supercritical CO_2, subcritical water [33], and microwave-assisted extraction [34].

Finally, the mass transfer kinetic of the HPCDAE for can be established through mathematical modeling for the varying type of plant samples. The knowledge of the extraction kinetics is vital for any future scaling up process [35].

9. CONCLUSION

The HPCDAE has shown a promising prospect as a rapid and efficient green extraction method for the extraction of phenolics. The process parameters have been established; however more additional parameters can be included to

further understand the extraction process, and to ultimately enhanced its performance. Moreover, mathematical modeling of the extraction kinetics is required for scale up process. It is hoped that this review will instigate more study into the extraction of bioactive compounds via HPCDAE in the future.

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